ÉTUDE SUR LA SANTÉ DANS LA RÉGION DE

Belledune

AREA HEALTH STUDY

Belledune • Petit-Rocher • Pointe-Verte

Appendix AC - Toxicity Profiles

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Appendix AC Toxicological Profiles

Toxicological profiles are compiled for all chemicals identified as Chemicals of Potential Concern (COPC). The objective of the toxicological profiles is to summarize the current literature with regard to potential effects including both carcinogenic and non-carcinogenic impacts. The toxicological profiles are not exhaustive reviews of the available literature but summarizes of the data provided by reliable agencies such as Health Canada, United States Environmental Protection Agency (U.S. EPA), World Health Organization (WHO) and the U.S. Agency for Toxic Substances and Disease Registry (ATSDR).

The toxicological profile examines the potential effects based on the route of exposure. For some contaminants the route by which the exposure is received has a direct impact on the endpoint of exposure. Evaluation of potential toxicity through inhalation and oral routes of exposure are typically conducted while information on dermal exposure is limited.

The quantity and quality of available information from human and animal studies varies widely from one contaminant to another, and it is thus it is sometimes only possible to present qualitative information on the toxicity of contaminants to humans. However, where available, in the literature, exposure limits can also be obtained. In general, information is provided for slope factors (SF) or unit risks (UR) to assess the potential carcinogenic risk and reference doses (RfD) or reference concentration (RfC) to assess the potential non-carcinogenic effects.

Slope Factor (SF) or Unit Risk (UR)

For evaluation of carcinogenic compounds slope factors or unit risks are derived to provide a plausible upper bound estimate of the probability of a response during a lifetime. For carcinogens that act by damaging the DNA no threshold is assumed to exist (i.e. every dose presents some risk).

Reference Dose (RfD) or Reference Concentration (RfC)

For many non-carcinogenic effects, protective biological mechanisms must be overcome before an adverse effect is manifested from chronic exposure to a toxicant. This is known as a "threshold" concept. Non-carcinogens are often referred to as "systemic toxicants" because of their effects on the function of various organ systems. A reference dose (RfD) or reference concentration (RfC) is the value most often used in the evaluation of non-carcinogenic effects resulting from exposure to toxicants. It represents an estimate of the daily exposure level for a chemical for the entire population, including sensitive receivers, that is not anticipated to present an appreciable risk of an adverse effect during a portion of a lifetime. Uncertainty factors are used in the development of the RfD and RfCs to address the uncertainties in

extrapolation of data, usually conducted in controlled experiments on animals, for use on human.

C1.0 Toxicological Profile for Arsenic

In its elemental form, arsenic (As) is a steel gray metal-like substance that is found naturally in the earth's crust. Arsenic has four oxidation states, (-3, arsine), (0, metal), (+3, arsenite) and (+5, arsenate), although it is usually found as inorganic arsenic sulphide or as metal arsenates and arsenides. Organic arsenic compounds can also form, but are typically less toxic than inorganic arsenic compounds. Arsenic compounds are mostly white or colourless, and tasteless. Arsenic compounds can have different solubilities in water and in acids. Compounds that contain arsenic are referred to as 'arsenicals.'

Inorganic arsenic occurs naturally in soil and rock, and erosion and weathering can release it into the aquatic and terrestrial environments. Anthropogenic activities that release arsenic into the environment include mining and processing of gold and base metal ores (including copper, lead, etc). Smelting of these ores can release arsenic into the air as a fine dust. Arsenic is also used extensively as a wood preservative, in the form of chromated copper arsenate. Other industrial and commercial uses of arsenicals include their use as alloys to improve other metals and in lead-acid batteries, as semi-conductors and diodes, and as pesticides in agriculture, principally in cotton fields and in orchards (ATSDR 2000). However, inorganic arsenicals have been banned from use in agriculture, and other arsenicals are now being used in their place. Arsenic is released into the air during fossil fuel combustion from sources such as coal-fired power generators, and is also released during waste incineration and disposal processes.

Exposure pathways for arsenic typically include air, water, food and soil *via* inhalation, ingestion and dermal exposure routes. Exposure pathways including the ingestion of fish, seafood and meat, and ingestion of soil and dust by children are likely to be the major source of intake. Exposure to arsenic in drinking water may be of concern in particular areas where bedrock contains naturally high levels of arsenic that can become dissolved in groundwater, leading to high levels in drinking water. Each exposure pathway can involve exposure to different forms of arsenicals with different bioavailabilities, which can have a large impact on differential uptake. For example, inorganic arsenic in drinking water is more bioavailable than organic arsenic in fish.

There is debate surrounding the essentiality of arsenic. There are animal data to support the hypothesis that arsenic is an essential element, but there are no data to support this theory in humans. The U.S. EPA (1988) concluded that if arsenic is an essential element, humans are exposed to sufficient amounts in the environment

because arsenic deficiencies are not seen.

C1.1 Pharmacokinetics

The absorption of arsenicals *via* oral exposure is largely dependent on its solubility in water, while the absorption of arsenicals *via* inhalation is dependent both on solubility and particle size. Dermal absorption of arsenicals is not well characterized, but it is thought to be a lot less significant than other exposure routes.

Different forms of arsenic can have very different solubilities *via* oral exposure. For example, when ingested, it is known through fecal tracer experiments that most of soluble pentavalent and trivalent arsenic is absorbed through the gastrointestinal (GI) tract. However, insoluble arsenicals such as arsenic sulfide and lead arsenate are absorbed to a much lesser extent *via* both oral and inhalation exposure routes. Arsenate and arsenite compounds are both quite soluble and are well absorbed *via* inhalation and oral exposure. Ingested elemental arsenic is not well absorbed in the GI tract, and arsenic oxide compounds are quite well absorbed (>80%) *via* oral exposure and less so *via* inhalation exposure (Health Canada 1989).

Following absorption, binding to hemoglobin in the blood allows arsenic to travel widely throughout the body. Within 24 hours following absorption, arsenic is distributed to the tissues of the liver, kidneys, lungs, spleen and skin (Wickstroem 1972), although it accumulates in the skin, bone and muscle. It is thought that inorganic arsenic does not cross the blood-brain barrier, but it is able to cross the placental barrier, exposing the developing fetus (Gibson and Gage 1982). Arsenic compounds can undergo redox reactions to form trivalent and pentavalent forms of arsenic in the body.

Upon ingestion, trivalent arsenic appears to undergo elimination from the body by two different mechanisms. The first is the rapid excretion of non-methylated arsenicals in both the trivalent and pentavalent forms in the urine. The second mechanism involves sequential methylation of trivalent arsenic into monomethylarsonic acid (MMAA) and dimethylarsinic acid (DMAA) in the liver (Lovell and Farmer 1985; Buchet and Lauwerys 1985), and subsequent rapid urinary excretion. Pentavalent arsenic must be reduced to trivalent arsenic before it can be excreted by this detoxifying mechanism, which appears to become saturated after the daily dose level exceeds 0.5 mg (Buchet *et al.* 1981). Secondary elimination pathways for inorganic arsenic include the feces, skin, hair, nails and sweat (ICRP 1975). Excretion of organic arsenic compounds is thought to occur rapidly, with most of the arsenic remaining unchanged (Health Canada 1989). Estimated half-lives of inorganic arsenic compounds range between 2-40 days in humans (Pomroy *et al.* 1980).

In vivo rodent studies have shown that arsenic can induce synthesis of the detoxifying metal-binding protein, metallothionein, although *in vitro* studies suggest it can bind to a much lesser extent than cadmium or zinc and only a small fraction of the administered arsenic binds to metallotheionein (ATSDR 2000). The more toxic the arsenic

compound, the greater its ability to induce metallothionein synthesis.

C1.2 Toxicology

Different forms of arsenic have different toxicities in humans. The most toxic form of arsenic in humans is arsine gas, followed by the trivalent arsenites, the pentavalent arsenates, and the organo arsenic compounds, in order of decreasing toxicity. Acute and chronic exposure to arsenicals result in different toxicological endpoints, as does chronic exposure *via* oral and inhalation routes. Animal data indicate that the possibility of health risks from organic arsenicals, especially those of methyl and phenyl arsenates, should not be disregarded because humans can be exposed to significant amounts due to their wide application in agriculture.

C1.2.1 Non-Cancer Effects

Oral exposure to arsenic can result in effects such as GI irritation, peripheral neuropathy, vascular lesions, anemia and skin disease. Data from people acutely exposed to contaminated well water show that arsenic can result in GI disturbances, pain, numbness and tingling in the extremities, muscle weakness and cramping, flushing and skin disorders (Health Canada 1989). The lethal dose for oral exposure to arsenic is thought to be between 50 to 300 mg. Severe effects following oral exposures as low as 20 mg have been shown, although people have also survived intakes of 10 g (Health Canada 1993).

Non-cancer health effects have been documented in studies of populations in Taiwan (Tseng 1977, Tseng *et al.* 1968), Chile (Zaldivar 1980, Zaldivar and Ghai 1980, Borgono and Greiber 1971), the United States (U.S.; Valentine *et al.* 1982), Mexico (Cebrian *et al.* 1983) and Canada (Hindmarsh *et al.* 1977), who were chronically exposed to arsenic in drinking water. Skin disorders such as skin lesions, hyperpigmentation, warts and hyperkeratosis were the most common health effect noted, and occurred after exposures of at least 5 years (Health Canada 1989). Other non-cancer health effects reported include peripheral neuropathy and peripheral vascular disease. Studies based on arsenic exposures *via* drinking water for an average of 7 years for a population in Antofagasta, Chile showed a wide range of health effects, to which children were particularly susceptible. Effects experienced by children under the age of 16 included skin disorders, effects on the respiratory system such as chronic coryza, cough, bronchopulmonary disease, effects on the cardiovascular systems such as myocardial infarction and peripheral vascular disorders, and GI disorders (Zaldivar 1980, Zaldivar and Ghai 1980). The largest epidemiological study on arsenic (as of Health Canada 1989) was conducted in Taiwan on a population exposed in well water (Tseng 1977). Results of the study showed a clear dose-response relationship between arsenic exposure and frequency of health effects that included dermal lesions and a peripheral vascular disorder called "blackfoot

disease" that results in gangrene of the foot. However, study results are somewhat ambiguous due to a number of confounding factors that included a failure to account for other sources of arsenic exposure to the population.

There is equivocal evidence from epidemiological studies that indicates that chronic exposure to arsenic *via* oral and inhalation may result in mortality due to cardiovascular and cerebrovascular causes (Health Canada 1993). A study performed in Nova Scotia on a small group of people exposed to arsenic at levels higher than 0.05 mg/L in well water showed some neurological effects (Hindmarsh *et al.* 1977), while other studies did not detect adverse neurological effects. Oral exposures to arsenic have resulted in hematological effects including anemia and leukopenia at acute, intermediate and chronic durations where dose levels exceeded 0.07 mg/kg-d (ATSDR 2000). Possibly reversible haematopoetic effects have also been reported following occupational exposures at unknown concentrations (Health Canada 1993). An unconfirmed study showed possible immune impairment following exposure through drinking water containing arsenic at levels of 0.39 mg/L (Health Canada 1993).

No conclusive evidence is available regarding possible reproductive effects from exposure to arsenic in drinking water. One study suggested a possible link between maternal exposure to arsenic in drinking water and increased occurrence of coarction of the aorta, a type of congenital heart disease (Zierler *et al.* 1988). However, many confounding factors were not accounted for in this study (HC 1993). Another study suggested there was an increased odds ratio for miscarriages due to arsenic exposure in drinking water (Aschengrau 1989), however this study also had confounders that made results inconclusive.

Based on limited studies in humans, inhalation exposures to arsenic can result in irritation of the respiratory tract, nausea and skin effects. Occupational studies have shown that workers chronically exposed to arsenic in air have experienced adverse dermatological effects including hyperkeratosis, hyperpigmentation and dermal lesions (British Industrial Biological Research Association 1990), and exposures to inorganic arsenic in air have resulted in irritation of the nose and throat, laryngitis, bronchitis and perforation of the nasal septum (ATSDR 2000). There is some evidence to suggest that inhalation exposures to arsenic trioxide dust could result in cardiovascular effects (MOE 2001).

There are a handful of studies that indicate that dermal exposure to arsenic can result in local irritation and dermatitis.

C1.2.2 Cancer Effects

Oral exposures to arsenic can result in effects that include skin cancer, bladder cancer, kidney cancer, liver cancer and lung cancer. Population-level studies in Taiwan documented occurrences of skin cancers including squamous cell carcinoma, basal cell carcinoma and Bowen's Disease in people chronically exposed to arsenic *via* drinking water for about 25 years (Tseng 1977, Tseng *et al.* 1968). In particular, the largest epidemiological study conducted on arsenic (as of Health Canada 1989) demonstrated a clear dose-response relationship between arsenic exposure in well water and the frequency of skin cancer (Tseng 1977). However, study results are ambiguous due to a number of confounding factors that included a failure to account for other sources of arsenic exposure to the population. Skin cancer and possibly cancers of other organs have been reported in populations in Chile (Zaldivar 1980, Zaldivar and Ghai 1980, Borgono *et al.* 1971), the U.S. (Valentine *et al.* 1982), Mexico (Cebrian *et al.* 1983) and Canada (Hindmarsh *et al.* 1977) who were chronically exposed to arsenic in drinking water.

Inhalation exposures to arsenic can result in an increased number of lung cancers in humans. Data from numerous epidemiological studies and case reports from workers in smelters and arsenical pesticide production plants have supported the association of inhalation exposure to inorganic arsenic and respiratory cancer. However, data from only three smelter studies were sufficient to derive a quantitative relationship between exposure and excess risk of respiratory cancer. Two of the studies, conducted at the Tacoma smelter in Washington and the Anaconda smelter in Montana, demonstrated a relationship between mortality due to respiratory cancer and arsenic exposure (Enterline *et al.* 1987; Higgins *et al.* 1986). However, smoking habits were possible confounding factors in both studies and in one study, exposure to sulfur dioxide was a possible confounder. The other study, conducted at the Ronnskar smelter in Sweden, demonstrated a relationship between mortality due to lung cancer and arsenic exposure, although the magnitude of exposure had a larger impact on mortality from lung cancer than duration of exposure. Again, smoking was a possible confounding factor (Jarup *et al.* 1989).

Health Canada (1993) has determined the group of inorganic arsenic compounds to be carcinogenic to humans, and to fall under Group I of their classification scheme. The U.S. EPA (2004) has deemed that there is sufficient weight-of-evidence to determine that inorganic arsenic is a human carcinogen (A).

C1.2.3 Susceptible Populations

Because arsenic is thought to be methylated in the liver during metabolism and because this is thought to affect its toxicity, populations especially susceptible to arsenicals may include individuals with a decreased methylation capacity. A decreased ability of the liver to methylate compounds could be due to a dietary deficiency in products containing choline or methionine, because these molecules are methyl donors. Genetic conditions that could impact the enzymes involved in methylation could also potentially result in an increased susceptibility to arsenic toxicity (ATSDR 2000).

C1.3 Current Exposure Limits

C1.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C1-1.

Non-Cancer

The U.S. EPA (2004) provide an oral reference dose (RfD) of 0.0003 mg/kg-d for inorganic arsenic, based on a LOAEL of 0.014 mg/kg-d for chronic oral exposure to arsenic in well water in a Taiwanese study (Tseng *et al.* 1968, Tseng 1977). The study could have also included other exposure pathways including food, thus the U.S. EPA (2004) assumed that arsenic through consumption of sweet potatoes and rice accounted for 0.002 mg/day, that water consumption was 4.5 L/day and that body weight was 55 kg. The toxicological endpoint is hyperpigmentation, keratosis and possible vascular complications. An uncertainty factor of 3 is used to account for human variability and due to the lack of data on reproductive toxicity. The overall confidence in this RfD is reported to be medium.

The ATSDR (2000) provide a minimal risk level (MRL) of 0.005 mg/kg-d for acute oral exposure to calcium arsenate, based on a LOAEL of 0.05 mg/kg-d from a study of human poisoning cases that represented an episodic exposure to soy sauce. The toxicological endpoints or critical effects are facial edema and GI symptoms. An uncertainty factor of 10 is used: 10 because a LOAEL is used to derive the MRL, and 1 to account for human variability.

The ATSDR (2000) provide a second MRL of 0.0003 mg/kg-d for chronic oral exposure to arsenic in well water in a Taiwanese study (Tseng 1977, Tseng *et al.* 1968), although it could have also included other exposure pathways including food. The MRL is based on a NOAEL of 0.0008 mg/kg-d, and the toxicological endpoint is skin lesions such as hyperpigmentation, keratosis, and dermal lesions, observed for the two LOAELS. An

uncertainty factor of 3 is used to account for human variability.

Health Canada (2003, 1996) does not provide exposure limits that address the non-cancer effects of arsenic. However, the Health Canada Food Directorate has adopted the provisional tolerable weekly intake (pTWI) of 15 µg/kg determined by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1988 (WHO 1996). This is equivalent to an RfD (or tolerable daily intake, TDI) of 0.002 mg/kg-d. The toxicological rationale for the selection of this RfD, including the endpoint, is not clear. However, the RfD is meant for chronic exposure as it is derived from a WHO TDI.

Cancer

The U.S. EPA (2004) provide an oral cancer slope factor of 1.5 per (mg/kg-d) and a drinking water unit risk of 0.05 per (mg/L) for skin cancer. This is based on a time and dose-related formulation of the multistage model applied to data from a chronic Taiwanese study of exposure to arsenic in drinking water (Tseng 1977, Tseng *et al.* 1968). Assumptions included that people were exposed to arsenic from birth, drinking water consumptions of 3.5 L/day for males and 2.0 L/day for females and that skin cancer risk was the same for people in the U.S. as in Taiwan. Doses were adjusted to account for differences in water consumption and body weight between the Taiwanese and U.S. populations. The U.S. EPA (2004) mention several uncertainties associated with use of this slope factor stemming from the Tseng *et al.* (1968) and Tseng (1977) study. These uncertainties included the fact that skin cancer rates could have been underestimated due to competing mortality from Blackfoot Disease, it is possible that the population was exposed to other sources of arsenic that were not accounted for in the slope factor (in media such as food), uncertainty regarding drinking water consumption, and the temporal variability of arsenic concentrations in some wells was not known.

The ATSDR (2000) provide cancer effect levels (CELs) ranging from 0.0075 mg/kg-d to 0.022 mg/kg-d for skin cancer risk resulting from chronic human exposure to arsenic compounds in drinking water. Exposure durations ranged from greater than one year to continuous exposure. Other CELs are provided for other cancer endpoints resulting from oral exposure to arsenic compounds, including bladder, lung, liver, kidney and urinary tract cancers.

Health Canada (1996) provide a Tolerable Dose$_{05}$ (TD_{05}) for arsenic of 0.844 mg/L for women and 0.905 mg/L for men, based on skin cancer risk from a Taiwanese epidemiological study of exposure to arsenic in drinking water (Tseng 1977, Tseng *et al.* 1968). Health Canada (2003) calculate the mean TD_{05} and converts it to an oral slope factor of 2.8 per (mg/kg-d) using a standard water intake rate of 1.5 L/day and a standard body weight of 70.7 kg. The toxicological endpoint considered was most likely skin cancer, however, this was not explicitly stated. In the most recent analysis of the data presented by Health Canada (2004), the cancer risk models based on Taiwanese data have been updated (Morales *et al.* (2000)). An evaluation was completed of the cancer potency indices for liver, lung, bladder and kidney cancers. The lifetime risks of

cancer in the general population in Canada associated with ingestion of 1 μg/L of arsenic in drinking water were estimated to be 4.5×10^{-6} (based on kidney cancer in men) to 2.2×10^{-5} (based on lung cancer in women) (Health Canada 2004). Based on the 95% upper-bound level, an oral slope factor of 1.2 $(mg/(kg\ d))^{-1}$ can be determined.

Table C1-1 Oral Exposure Limits for Arsenic Compounds

Arsenical	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Calcium arsenate	0.005 mg/kg-d	Acute	Facial edema, GI symptoms (human)	ATSDR 2000
Arsenic	0.0003 mg/kg-d	Chronic	Hyperpigmentation, keratosis, dermal lesions (human)	ATSDR 2000
Inorganic arsenic	0.0003 mg/kg-d	Chronic	Hyperpigmentation, keratosis and possible vascular complications (human)	U.S. EPA 2004
Arsenic	0.002 mg/kg-d	Chronic	Not readily available	WHO 1996 and Health Canada Food Directorate
Cancer Effects				
Arsenic compounds	0.0075 – 0.022 mg/kg-d	Chronic	Skin cancer (human; cancer effect level)	ATSDR 2000
Inorganic arsenic	1.5 per (mg/kg-d)	Chronic	Skin cancer (human)	U.S. EPA 2004
Arsenic	2.8 per (mg/kg-d)	Chronic	Skin cancer, although not explicity stated (human)	Health Canada 2003
Arsenic	1.2 per (mg/kg-d)	Chronic	Lung cancer (human)	Health Canada 2004

C1.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C1-2.

Non-Cancer

The ATSDR, U.S. EPA and Health Canada do not provide exposure limits for non-cancer health effects resulting from inhalation exposure to arsenic.

Cancer

The U.S. EPA (2004) provide an inhalation unit risk of 4.3 per (mg/m^3). This is based on occupational studies of male workers at the Anaconda smelter in Montana and at the Tacoma ASARCO smelter in Washington who showed an increased risk of developing lung cancer following inhalation exposures to arsenic. The extrapolation method used to generate the slope factor was the absolute-risk linear model, and a

geometric mean of the different unit risks from each study was used to derive the U.S. EPA (2004) unit risk. This unit risk should not be used if the air concentration exceeds 0.002 mg/m^3, since it may not be appropriate above this concentration.
The ATSDR (2000) provide cancer effect levels (CELs) ranging from 0.05 mg/m^3 to 0.38 mg/m^3 for lung cancer risk resulting from chronic human exposure to trivalent arsenic (As+3). Exposure durations ranged from 3 months to 30 years.

Health Canada (2003) provide an inhalation slope factor of 28 per (mg/kg-d). This was derived from Health Canada (1993), in which they present 3 different TD_{05} of 7.83, 10.2 and 50.5 mg/m^3 based on the three previously mentioned occupational studies of smelter workers at the Tacoma, Anaconda and Ronnskar smelters. Dose-response curves were constructed for the three studies, and along with age-adjusted lung cancer mortality rates for Canadians, were used to determine excess risk of respiratory cancer. The slope factor is derived from these three TD_{05}s, but it is not clear exactly how.

Table C1-2 Inhalation Exposure Limits for Arsenic Compounds

Arsenicals	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Arsenic	--[1]	--	--	--
Cancer Effects				
Trivalent arsenic (As+3)	0.05 – 0.38 mg/m^3	Varied	Lung cancer (human; cancer effect level)	ATSDR, 2000
Inorganic arsenic	4.3 per (mg/m^3) or 15 per (mg/kg-d)	Chronic	Lung cancer (occupational)	U.S. EPA 2004
Arsenic	28 per (mg/kg-d)	Chronic	Respiratory cancer (occupational)	Health Canada, 2003

Note: -- No data

C1.3.3 Selected Exposure Limits

Table C1-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C1-3 Selected Exposure Limits for Arsenic for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Arsenic	oral	non-carcinogenic	0.002	mg/kg/d	Not known	Health Canada Food Directorate
	oral	carcinogenic	1.2	$(mg/kg/d)^{-1}$	Lung cancer	Health Canada 2004
	inhalation	carcinogenic	28	$(mg/kg/d)^{-1}$	Lung cancer (inhalation, human occupational exposure)	Health Canada 2003

C1.4 References

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C2.0 Toxicological Profile for Cadmium

Cadmium (Cd) is a soft and silver white metal that is naturally occurring in the earth's crust. Cadmium is commonly found as a mineral combined with other elements such as cadmium oxide, cadmium chloride, cadmium sulfate and sulfide and cadmium carbonate. In nature, cadmium is most frequently found as a mineral bound to other metals such as zinc, lead and copper. For this reason, cadmium is typically mined along with other metals. Cadmium is used in industry and in consumer products, mostly having to do with batteries, pigments, metal coatings, plastics and metal alloys. In this report, "cadmium compounds" refers to inorganic cadmium minerals, and excludes organic cadmium compounds.

Cadmium compounds dissolve in water to different degrees, and typically the cadmium sulfates and chlorides are most hydrophilic. Natural activities that emit cadmium into the environment include weathering of soil, till and bedrock, forest fires and volcanic eruptions. Anthropogenic sources of cadmium emissions include: mining activities including metal smelting and refining, stationary and mobile sources of fossil fuel combustion, burning of household waste, sewage sludge application and application of fertilizers to crops.

Potentially important human exposure pathways for cadmium include food ingestion and tobacco smoking. Leafy vegetables, potatoes and shellfish are reported to contain the highest levels of cadmium, while tobacco smoking can contribute substantially to cadmium intake; some smokers may double their daily intake of cadmium compared to the general population. Other possible exposure pathways include inhalation, soil and water ingestion.

C2.1 Pharmacokinetics

Cadmium absorption and distribution can be greatly affected by the route of exposure and the form of the cadmium compound. However, the mechanism of action *via* the cadmium cation is the same.

Absorption of cadmium *via* ingestion of food or water is about 5% (Health Canada 1986 states 4-7%), with most cadmium passing through the gastrointestinal (GI) tract without undergoing absorption. Cadmium can also be ingested *via* mucociliary clearance from the lungs. During absorption, or cadmium uptake, cadmium passes from the lumen to the mucosa, and then passes into the blood. Absorption of cadmium in the GI tract can be affected by interactions with other metals, such as iron, calcium, chromium, magnesium and zinc, or proteins, such as glutathione and sulfhydryl containing

enzymes. These interactions can take place in the food or water that has been ingested, or within the body's cells. Levels of metals and proteins in the body can vary with age and physiological status – for example, nutritional deficiencies in iron or calcium can result in higher uptake of cadmium (ATSDR 1999).

Upon inhalation, a fraction of inhaled particles are deposited in the respiratory tract, while the rest are exhaled. Fine particles that are inhaled tend to penetrate deeply into the lungs and are deposited in the alveoli, while larger particles tend to remain in the upper airway and are often removed from the lungs through mucociliary clearance. Cadmium compounds in air are typically associated with fine suspended particulate matter, and thus a fraction of inhaled cadmium is able to reach the alveoli, where absorption occurs. A smaller fraction remains in the upper airway where some absorption may occur for the soluble cadmium compounds. Absorption of inhaled cadmium compounds is about 25%, while absorption of cadmium inhaled during smoking may be higher due to the abundance of fine particles (ATSDR 1999).

Dermal absorption of cadmium compounds is very small, at about 0.5%.

The majority of absorbed cadmium accumulates in the liver and kidneys. The kidneys will accumulate more cadmium than the liver during chronic exposures to lower doses, while the liver may accumulate more during acute exposures to high doses. Very little cadmium is contained in the liver and kidneys of neonates, and cadmium accumulates in these organs with increasing age.

Following absorption, the cadmium ion (+2) is not thought to undergo any direct metabolic conversion. It is circulated throughout the body bound to the plasma protein carrier albumin, where it reaches the liver. The liver contains an abundance of metallotheionein (detoxifying metal-binding proteins), which bind cadmium. Metallotheionein-bound cadmium then re-enters the blood, where it travels to the kidneys. The current hypothesis is that lysosomes in the kidneys break down this complex, releasing free cadmium into the kidney, where it induces synthesis of metallotheionein in the kidney. Metallotheioneins in other tissues of the body are also thought to be inducible when exposures to cadmium (and other metals, organics or physiological stresses) occur. For example, metallotheionein induction can occur in the lungs following inhalation of cadmium, and can also occur in the intestine following ingestion of cadmium (ATSDR 1999).

Directly ingested cadmium, or cadmium that has been ingested following clearance from the lungs, that is not absorbed is mainly eliminated in the feces, while absorbed cadmium is slowly eliminated through the feces and urine. About 50% of maternal cadmium has been shown to pass through the placenta to the fetus, while 5% to 10% of cadmium in the nursing mother's blood can be excreted in breast milk (ATSDR 1999).

Cadmium can remain in the body for a long time; animal studies show half-lives from several months to several years. Estimates of half-lives for cadmium in the human kidneys have ranged from 6 to 38 years, while those for the human liver have ranged from 4 to 19 years (ATSDR 1999).

C2.2 Toxicology

It is thought that when metallotheionein proteins become saturated with cadmium (and other ligands) and excessive quantities of free cadmium arise in the kidney, renal damage can result. As such, cadmium toxicity is thought to be related to the unbound free cadmium ions. Metallothioneins are involved in cadmium detoxification processes, and the body has a way of self-regulating cadmium levels – induction of cadmium-binding metallotheionein synthesis when levels become high, and no induction when levels are low.

C2.2.1 Non-Cancer Effects

Acute inhalation or oral exposures to cadmium in both humans and animals can result in death through the destruction of cell membranes at the point of entry. Acute inhalation exposures to cadmium in both humans and animals can result in respiratory effects such as pulmonary edema, bronchitis pneumonitis or long term lung impairment, by destruction of lung epithelial cells. Longer term inhalation exposures to cadmium can result in decreased lung function, emphysema and damage to olfactory function. Animal and human studies regarding the potential cardiovascular effects of cadmium are inconclusive (ATSDR 1999).

Acute exposures to high levels of cadmium *via* oral exposure can result in GI effects resulting from irritation of the gastric epithelial cells. This can produce symptoms such as nausea, vomiting and abdominal pain.

Oral and inhalation exposures to cadmium can result in anemia in both humans and animals, which is speculated to be due to decreased iron uptake.

Chronic exposure to cadmium *via* inhalation or ingestion at levels that can lead to kidney damage may result in muskuloskeletal effects such as bone disease in susceptible individuals. Chronic exposure to cadmium at lower levels may result in osteoporosis *via* alterations in kidney metabolism of vitamin D (Kido *et al.* 1990, Nogawa *et al.* 1987, 1990, Blainey *et al.* 1980).

Only exposures to high levels of cadmium have been shown to result in liver damage in animals, while liver effects in humans have not been demonstrated from either inhalation or oral exposures. It is hypothesized that the liver's resistance to cadmium

toxicity may be due to its ability to synthesize more metallotheionein, with which it binds excess cadmium.

Chronic and intermediate inhalation and oral exposures to cadmium in both humans and animals can result in kidney effects, and the kidney is the main target organ for cadmium toxicity for exposures of this nature. Kidney damage first occurs in the renal tubules, resulting in an increase of tubular proteinuria (decreased resorption of low molecular weight proteins). The extent of kidney damage from cadmium exposure is dose-dependent. At high doses, when the concentration of cadmium ion in the kidney exceeds the binding capacity of metallotheionein proteins, and the synthesis of new metallotheionein to bind excess cadmium occurs, renal damage from the cadmium free ion may commence. However, chronic exposure to low doses of cadmium can also result in renal damage – signaling that metallotheionein-bound cadmium can produce renal damage through different toxicity mechanisms. Although tubular proteinuria is not a particularly adverse effect, studies have suggested that kidney damage from cadmium exposure may interfere with vitamin D metabolism (Buchet *et al.* 1990, Nogawa *et al.* 1990, Kido *et al.* 1989), which could lead to a decrease in bone density, especially in elderly women (ATSDR 1999).

Acute inhalation exposure to high levels of cadmium in animals but not in humans has shown significantly reduced body weights. Acute oral exposure to cadmium in animals has also shown decreased body weights and rates of growth, and intermediate oral exposures in animals have shown reductions in body weight. High doses at chronic exposures caused decreased growth rates and body weights in animals.

There is conflicting evidence regarding the immunological effects of cadmium. Inhalation exposures to cadmium in humans have not documented immunological effects, but oral exposure studies are lacking. In animals, both inhalation and oral exposures have resulted in immunological effects. Studies are lacking regarding the neurological effects of cadmium in humans.

There is conflicting evidence regarding the reproductive effects of cadmium following inhalation exposures. Some human studies have shown a reduction in sperm number or *via*bility, while others showed no effect on male fertility, male hormone levels, sperm density or semen quality. Animal studies did not demonstrate a loss of reproductive success. Oral exposure studies in humans are lacking, but animal data have shown adverse reproductive effects for both males and females.

Few human studies have examined the developmental effects of cadmium, and those that did were plagued with confounding factors. Animal studies have demonstrated that cadmium is a developmental toxin *via* inhalation, oral and parenteral exposure routes (Baranski 1987, 1985, Prigge 1978b), producing effects such as decreased fetal weight, skeletal malformations and impaired neurological development.

Studies exploring the potential genotoxicity of cadmium *via* inhalation and oral exposures have produced conflicting results.

There is little information available on cadmium toxicity following dermal exposure.

C2.2.2 Cancer Effects

A handful of human studies have examined the potential carcinogenicity of cadmium *via* oral exposures, but none have shown an increase in cancer. However, these studies were limited by a lack of reliable individual dose estimates and thus are of limited sensitivity to detect a carcinogenic effect.

There is conflicting evidence regarding the potential for cadmium to result in lung and prostate cancer from inhalation exposure in humans. Several occupational studies have examined the relationship between lung cancer and inhalation exposures, but the results are difficult to interpret due to a lack of control of confounding factors and a small number of cancer mortality cases in the United States (U.S.) only. Occupational studies conducted outside of the U.S. did show an association between cadmium and lung cancer, but could not quantify a dose-response relationship, and smoking was a confounding factor. Results from occupational studies that explored the relationship between prostate cancer and inhalation exposures also produced conflicting results, although Kazantzis *et al.* (1992) conducted a 5-year study of workers in England and also a review of existing data and concluded that cadmium exposure does not appear to cause prostate cancer.

Animal studies have only shown a convincing relationship between cadmium exposure and increases in lung cancer in rats, and not in mice or hamsters. Most animal studies did not shown an increase in cancer resulting from oral cadmium exposures (ATSDR 1999).

Based on an assessment of sufficient evidence for carcinogenicity in human and animal studies, IARC has determined that cadmium is carcinogenic to humans. The U.S. EPA has determined that cadmium is a probable human carcinogen (B1) by inhalation, while there is not enough information to determine whether cadmium in water and food is also a human carcinogen. In the Canadian Environmental Protection Act Environmental Assessment report for inorganic cadmium compounds, Health Canada (1994) concludes that inorganic cadmium compounds are considered to be probably carcinogenic to humans based on inhalation studies performed on animals, and to fall under Group II of their classification scheme.

C2.2.3 Susceptible Populations

Populations who may be susceptible to cadmium toxicity have not been explicitly studied, but inferences can be made based upon the current knowledge of the mechanisms of cadmium toxicity. Individuals who are deficient in certain minerals such as iron and calcium, either due to an inadequate diet or repeat pregnancies, may experience greater cadmium absorption from the GI tract.

Animal studies have shown that individuals whose diet is deficient in calcium can experience increased bone absorption, sometimes producing a condition similar to 'Itai-Itai' ('ouch-ouch') bone and kidney disease. Further animal studies have shown that young animals are more susceptible to greater cadmium absorption in the GI tract and bone damage from cadmium. Thus, infants and children may be more susceptible to these effects as well.

Individuals with pre-existing kidney damage may experience the nephrotoxic effects of cadmium at lower doses than healthy adults. Pre-existing kidney damage can be caused by diabetes, exposure to drugs and chemicals, and the decline in kidney function that occurs with age (ATSDR 1999).

C2.3 Current Exposure Limits

C2.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C2-1.

Non-Cancer

The U.S. EPA (2004) provide an oral reference dose (RfD) of 0.0005 mg/kg-d for exposure *via* water, and an oral RfD of 0.001 mg/kg-d for exposure *via* food. Different RfDs are provided to account for differences in absorption in these different media. Both RfDs are based on chronic human occupational studies and an endpoint of significant proteinuria. The water RfD is based on a NOAEL of 0.005 mg/kg-d, while the food RfD is based on a NOAEL of 0.01 mg/kg-d, and both used an uncertainty factor of 10 to account for human variability. A toxicokinetic model was used to determine the highest exposure level at which no effect occurred. The overall confidence in the RfD is reported to be high.

The ATSDR (1999) provide an oral minimal risk level (MRL) of 0.0002 mg/kg-d for chronic exposure to cadmium in rice based on a NOAEL of 0.0021 mg/kg-d from an epidemiological study done in an area of Japan with elevated cadmium levels. The

endpoint is kidney damage in the form of proteinuria. An uncertainty factor of 10 is used to account for human variability.

Health Canada (2003) provide an oral tolerable daily intake (TDI) of 0.0008 mg/kg-d based on Health Canada (1986). This value is based on the World Health Organization's (1972) provisional permissible intake of cadmium.

Cancer

The U.S. EPA (2004) does not provide a slope factor for oral exposure to cadmium. The seven available animal studies of oral exposure to various cadmium compounds have shown no evidence of carcinogenic response.

The ATSDR (1999) provides only a single cancer effect level (CEL) of 3.5 mg/kg-d for oral exposures to cadmium. The CEL is based on a chronic study where male rats were exposed to cadmium chloride in their food, and the cancer endpoint is increased rates of prostatic adenomas.

Health Canada (2003) does not provide exposure limits for cadmium for cancer from oral exposures.

Table C2-1 Oral Exposure Limits for Cadmium and Cadmium Compounds

Cadmium Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Cadmium	0.0005 mg/kg-d (water)	Chronic	Significant proteinuria (occupational)	U.S. EPA 2004
Cadmium	0.001 mg/kg-d (food)	Chronic	Significant proteinuria (occupational)	U.S. EPA 2004
Cadmium	0.0002 mg/kg-d	Chronic	Proteinuria (epidemiological)	ATSDR 1999
Cadmium	0.0008 mg/kg-d	Based on WHO (1972) provisional permissible intake		Health Canada 2003
Cancer Effects				
Cadmium chloride	3.5 mg/kg-d	Chronic	Prostate cancer (rat; Cancer Effect Level)	ATSDR 1999

C2.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C2-2.

Non-Cancer
The ATSDR, U.S. EPA and Health Canada do not provide exposure limits for non-cancer health effects resulting from inhalation exposure to cadmium.

Cancer
The U.S. EPA (2004) provide an inhalation unit risk of 1.8 per (mg/m^3) based on an occupational study of adult male workers. The cancer endpoint was deaths from lung, trachea and bronchus cancers. A two-stage extrapolation model was used. It should be noted that this unit risk should not be used if the air concentration exceeds $6x10^{-3}$ mg/m^3. The effects of arsenic and smoking were not confounding factors as they were accounted for in the quantitative analysis for cadmium effects.

The ATSDR (1999) does not provide cancer exposure ICELs for inhalation exposure to cadmium.

Health Canada (2003) provide an inhalation unit risk of 9.8 per (mg/m^3) and an inhalation slope factor of 42.9 per (mg/kg-d). These exposure limits were calculated from the tolerable dose$_{05}$ (TD_{05}) derived in Health Canada (1994). The TD_{05} is based on a chronic study where rats were exposed to cadmium chloride aerosols *via* inhalation, which provided a clear dose-response relationship between lung tumour incidence and cadmium exposure (Oldiges *et al.* 1984, Takenaka *et al.* 1983). A multistage model was applied to the rat data, and exposure was amortized for the rat's lifetime, adjusted for experiment duration, and converted using factors that accounted for the physiological differences between rats and humans. Similar TD_{05} were calculated for rats inhaling cadmium compounds, including cadmium chloride, cadmium oxide dust, cadmium sulfate and cadmium sulfide.

Table C2-2 Inhalation Exposure Limits for Cadmium and Cadmium Compounds

Cadmium Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Cadmium	--[1]	--	--	--
Cancer Effects				
Cadmium	1.8 per (mg/m^3) or 6.3 per (mg/kg-d)	Chronic	Death from respiratory cancer (occupational)	U.S. EPA 2004
Cadmium chloride	9.8 per (mg/m^3)*	Chronic	Lung tumours(rat)	Health Canada 2003
Cadmium chloride	42.9 per (mg/kg-d)*	Chronic	Lung tumours(rat)	Health Canada 2003

Note: --[1] No data
* similar values derived for cadmium oxide, cadmium sulphate and cadmium sulphide

C2.3.3 Selected Exposure Limits

Table C2-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study. Since ingestion of cadmium via food sources is the primary route of exposure for this assessment, the TRV for oral exposure for food suggested by U.S. EPA (2004) was used.

Table C2-3 Selected Exposure Limits for Cadmium for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Cadmium	oral	non-carcinogenic	0.001	mg/kg/d	Significant proteinuria (Human study, occupational exposure)	U.S. EPA 2004
	inhalation	carcinogenic	42.9	(mg/kg/d)$^{-1}$	Lung cancer (inhalation, rat)	Health Canada 2003

C2.4 References

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C3.0 Toxicological Profile for Total Chromium

Chromium (Cr) is an element of natural and anthropogenic origin. Naturally occurring chromium is found in rock, flora and fauna and volcanic dust and gases. Chromium is found in several different oxidation states, or forms, including the most common metallic chromium (Cr(0)), trivalent chromium (Cr(III)) and hexavalent chromium (Cr(VI)) compounds. Some chromium such as chromium (III) is naturally occurring, but chromium (VI) and (0) compounds are mostly of anthropogenic origin. Anthropogenic sources of chromium to the environment include fossil fuel combustion, iron and steel production, waste from the chemical industry and transportation-related sources. Chromium compounds mainly in the (III) and (VI) forms are used in the chemical industry in chrome plating, dye and pigment manufacture, leather tanning (Cr(III) compounds) and wood preserving (Cr(VI) compounds). Further sources include drilling muds, rust and corrosion inhibitors, textiles and copying machine toner (ATSDR 2000; Health Canada 1994). In this report, the group of trivalent chromium compounds are referred to as "Cr(III) compounds," the group of hexavalent chromium compounds are referred to as "Cr(VI) compounds" and metallic chromium is referred to as "Cr(0)."

Potential human exposure pathways for chromium include ingestion of food, soil and water, as well as inhalation, tobacco smoking and skin contact. Chromium (III) is naturally present in many fresh vegetables, fruits, meat, yeast, and grain. The use of consumer products treated with chromium compounds such as household utensils, wood preservatives, cement, cleaning products, textiles and tanned leather may also lead to further exposure (ATSDR 2000). Occupational exposures to chromium compounds may occur in stainless steel welding, chromate production, chrome plating, the ferrochrome industry, the production of chrome pigments, copying machine maintenance, leather tanning, painting, battery making, candle making, dye making, printing, rubber making and cement production (ATSDR 2000).

At low levels, chromium (III) is an essential micronutrient for humans, while at higher levels it has been associated with adverse health effects. Chromium (III) promotes the action of insulin in the human body, enabling the metabolism of proteins, fats and sugars. Chromium (III) is thought to form a glucose tolerance factor (GTF) complex with nicotinic acid and possibly other amino acids, insulin and the cell membrane, thus acting as an insulin potentiator (Health Canada 1986). Chromium (VI) is not a micronutrient, and there are no known benefits associated with low dose exposures.

C3.1 Pharmacokinetics

Compared to Cr(III) compounds, Cr(VI) compounds are more readily absorbed by biological membranes. Estimates of absorption in the gastrointestinal (GI) tract following ingestion range up to 3% for Cr(III) compounds, and up to 10% for Cr(VI) compounds. Absorption of organic chromium complexes can be even greater. Prior to and following absorption of Cr(VI) compounds in the GI tract, it is rapidly reduced to Cr(III). Gastric juice can partially reduce Cr(VI) to Cr(III) prior to absorption in the GI tract.

Absorption of inhaled Cr(III) and Cr(VI) is up to 12% and 30%, respectively. Some Cr(VI) may be reduced to Cr(III) in the epithelial cells lining the lung. Inhaled chromium may also be absorbed in the GI tract from particles cleared from the lungs through mucociliary clearance.

Dermal absorption of chromium compounds depends on the properties of the particular chromium compound, the exposure medium, and the condition of the skin. Dermal absorption is greater for damaged skin. Health Canada (2003a) provides a relative dermal absorption factor of 0.09 for Cr(VI) compounds and 0.04 for Cr(III) compounds.

Absorbed chromium compounds are transported all over the body, including across the placenta to the fetus. In humans, chromium compounds can be stored in the skin, muscle, fat and lungs.

Chromium (VI) is unstable upon absorption into the body, and is reduced to other intermediate chromium species including Cr(V) and Cr(IV) and finally to Cr(III) by several compounds including ascorbate, glutathione or amino acids (ATSDR 2000).

Excretion of absorbed chromium occurs *via* the urine, while unabsorbed chromium is mainly eliminated *via* the feces. Excretion *via* hair and nails are also minor pathways. The half-time for excretion of potassium chromate in humans is 35-40 hours, and for most chromium compounds appears to be in the order of hours.

C3.2 Toxicology

Chromium (VI) is the most toxic form of chromium in humans, and is most easily absorbed through biological membranes due to its tetrahedral structure, similar to other natural anions. Chromium (III), on the other hand, has an octahedral structure that prevents it from easily moving across the cell membrane and which may be related to its lower toxicity. It is thought that the generation of free radicals during Cr(VI) reductions following absorption are what lead to its toxic effects, while reductions

occurring before absorption are thought to protect against the harmful effects of Cr(VI). Chromium (III) may be able to generate free radicals to a lesser extent than Cr(VI), but this is unlikely to occur under physiological conditions. The generation of free radicals, which can lead to cellular and DNA damage, may be linked to the toxicity of chromium compounds. It is difficult to distinguish between the toxic effects of Cr(III) and (VI) because reduction of (VI) to (III) occurs immediately preceding or following absorption (ATSDR 2000).

C3.2.1 Non-Cancer Effects

Deficiencies in chromium (III) intake can lead to weight loss, decreased growth, nervous system dysfunction, a condition similar to diabetes, and may be linked to atherosclerosis (ATSDR 2000).

Acute and sub-chronic oral exposures to Cr(III) compounds in rats and rabbits have resulted in decreased weights of the spleen and liver, and alterations in alveolar macrophages, respectively (Health Canada 1994).

Acute oral exposures to Cr(VI) compounds in humans have resulted in GI tract damage, respiratory damage, and death. Acute oral exposures to Cr(VI) compounds in animals have been associated with liver, kidney and hematological changes. Oral exposure of mice to Cr(VI) compounds through the diet for 7 weeks was noted to cause a decrease in sperm, while reproductive effects were noted in female mice exposed to potassium dichromate for 20 days in drinking water (ATSDR 2000). Chronic oral exposure to chromium compounds in food and drinking water in rats, mice and dogs did not result in any adverse effects or tumour increases (ATSDR 2000).

Acute inhalation exposures to Cr(VI) compounds in animals have been associated with inflammatory changes in the respiratory tract and macrophage changes. Epidemiological studies of workers occupationally exposed to chromium compounds including Cr(VI) compounds have shown some relationship between exposure and mortality due to non-neoplastic respiratory disease (Health Canada 1994). Further occupational studies have shown an association between exposure to low levels of Cr(VI) and Cr(III) compounds and non-fatal respiratory effects including nasal ulceration and septum perforation, coughing, sneezing, nasal irritation and bleeding, phlegm production, hemoptysis, bronchial asthma and bronchitis and decreased pulmonary function. The relationship between occupational exposures to Cr(VI) compounds and kidney damage or dysfunction is inconclusive, as is the relationship between exposures to Cr(0) and Cr(III) compounds and kidney dysfunction (Health Canada 1994).

In humans, inhalation of Cr(VI) compounds in different forms can result in different health endpoints; inhalation of Cr(VI) trioxide and soluble Cr(VI) salt aerosols can cause nasal damage, while inhalation of insoluble Cr(VI) compounds can lead to lower respiratory tract damage (ATSDR 2000). For this reason, some regulatory agencies

(e.g. the U.S. EPA) have included two separate exposure limits for different Cr(VI) compounds.

Chromium (VI) compounds have been documented to cause skin ulceration and contact allergic dermatitis in occupationally exposed workers and in data from case reports, while Cr(III) compounds are reported to be a less potent skin sensitizer (Health Canada 1994).

C3.2.2 Cancer Effects

Studies on the potential carcinogenicity of Cr(VI) compounds *via* oral exposure pathways in humans and animals are negative or inconclusive (ATSDR 2000).

Occupational data suggest that inhalation exposure to chromium compounds can lead to increased risk of respiratory system cancers, including bronchogenic and nasal cancers. Particular occupational group studies that supported an increased risk for respiratory systems cancer from chromium compounds (including Cr(III), Cr(VI) and Cr(0)) exposure include: chromate production workers (both (VI) and (III)), chromate pigment industries (mainly (VI)) and chrome platers (some (VI), nickel). Studies amongst stainless steel welders ((VI) and other chemicals) and ferrochromium alloy workers ((0), (III) and (VI)) were inconclusive (ATSDR 2000). A study of Icelandic masons exposed to Cr(VI) compounds (and other metals) showed an increase in mortality due to respiratory and urinary tract cancers (Rafnsson and Jóhannesdóttir 1986). Another occupational study amongst multiple industry workers in Montreal showed a significant relationship between occupational exposure to Cr(VI) compounds and lung and kidney cancers (Siemiatycki 1991) (Health Canada 1994).

Convincing evidence supporting the carcinogenicity of Cr(III) and Cr(0) compounds in humans is lacking. Occupational studies amongst leather tanners (where exposure was just to Cr(III) compounds) did not show an excess cancer risk. One study in Ontario gold miners did demonstrate an increased risk of mortality due to stomach cancer from exposure to Cr(III) compounds based on an indirect measure of cumulative chromium exposure (Kusiak *et al.* , 1993), but this relationship has yet to be confirmed by other analytical studies. Several studies in ferrochromium alloy workers did not demonstrate an association between chromium exposures (mainly in the (III) and (0) forms) and incidence or mortality due to respiratory cancers. A study in nickel/chromium foundry workers demonstrated an association between exposure to (mostly) Cr(0) and cancers of the gastrointestinal (GI) tract (Health Canada 1994).

Chronic inhalation studies in rats and mice provide further support for the carcinogenicity of Cr(VI) compounds; mice exposed to calcium chromate and rats exposed to sodium dichromate, both experienced increased incidence of lung tumours compared to controls (ATSDR 2000). Chronic inhalation studies in rodents exposed to a mixture of Cr(VI) and Cr(III) compounds showed slight increases in tumour incidence, but these effects could not be equivocally attributed to Cr(III) exposure (Health Canada 1994). Health Canada (1994) considers that animal data regarding the carcinogenicity

of inhaled Cr(VI) compounds suggest there is a risk of small increases in the incidence of lung tumours.

Chronic rodent oral exposures to Cr(III) compounds in food and drinking water did not result in any excess tumours at any site, although the study design was considered inadequate for the assessment of potential carcinogenicity. One study of oral exposure to Cr(III) compounds in mice did demonstrate non dose-related changes in hematological and biochemical parameters.

Genotoxicity studies of Cr(VI) compounds have been consistently positive in several assays, while Cr(III) compounds have not caused genotoxicity in human or animal cells. It is speculated that the reduction reactions of Cr(VI) compounds are required for genotoxicity to occur.

Jones (1990) and De Flora *et al.* (1989) have hypothesized a threshold for the carcinogenicity of Cr(VI) compounds. The premise is that gastric juices and mucosal linings have a limited capacity for extracellular reduction of Cr(VI) compounds to Cr(III) compounds prior to absorption, and are thus able to reduce a limited amount of Cr(VI) as a protective mechanism.

There is consensus between regulatory agencies that the weight of evidence supports the classification of inhaled Cr(VI) compounds as carcinogens. Stemming from both occupational and animal data, IARC has determined that the following Cr(VI) compounds are carcinogenic to humans: calcium chromate, zinc chromate, strontium chromate, and lead chromate. There are also limited animal data to suggest that chromium trioxide (chromic acid) and sodium dichromate are also carcinogenic. The U.S. EPA has determined that Cr(VI) in air is carcinogenic to humans (Group A), while there is not enough information to determine whether Cr(VI) in water and food is also a human carcinogen. Furthermore, the U.S. EPA has concluded that there are inadequate data to determine the potential carcinogenicity of insoluble salts of Cr(III) *via* ingestion or inhalation.

In their Canadian Environmental Protection Act Environmental Assessment report for chromium compounds, Health Canada (1994) concludes that Cr(VI) compounds are carcinogenic to humans based on epidemiological studies for exposed workers, and to fall under Group I of their classification scheme. The same report concludes there are insufficient available data to assess the carcinogenicity of Cr(III) compounds in humans.

C3.2.3 Susceptible Populations

Acute animal inhalation, oral and dermal exposure studies have identified female animals are potentially more sensitive to the lethal effects of Cr(VI). It is unclear whether this is also true for human females. Individuals more susceptible to the toxic effects of Cr(VI) include individuals with a decreased capacity to reduce Cr(VI) in the bloodstream. Furthermore, some sensitive individuals may develop asthma as part of an anaphylactic response to chromium exposure *via* inhalation. Smokers and those exposed to second hand smoke may also be at increased risk for lung cancer from chromium exposure due to pre-existing metaplastic changes in the respiratory mucosa.

C3.3 Current Exposure Limits

C3.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C3-1.

Non-Cancer

Cr(VI) Compounds
The U.S. EPA (2004) provide a chronic oral reference dose (RfD) of 0.003 mg/kg-d for soluble salts of Cr(VI) based on an adjusted NOAEL of 2.5 mg/kg-d from a rat drinking water study. An uncertainty factor of 300 is used to account for inter-species and human variability as well as conversion to a chronic, lifetime exposure limit, and a modifying factor of 3 is used for study uncertainty. The overall confidence in the RfD is reported to be low.

The ATSDR (2000) do not provide a minimal risk level (MRL) for reproductive and developmental effects from oral exposures to Cr(VI) compounds, stating that the available data are either insufficient or too contradictory. However, they do provide a provisional guideline for Cr(III) and (VI) based on the safe daily dietary intake of 0.003 mg/kg-day for a 70 kg individual (NRC 1989).

Health Canada (2003b) provide an oral non-carcinogenic tolerable daily intake (TDI) of 0.001 mg/kg-d for Cr(VI) compounds, based on the Canadian Guidelines for Drinking Water Quality listed in Health Canada (1986). The toxicological rationale for the selection of this TDI, including the endpoint, is not clear.

Cr(III) Compounds
The U.S. EPA (2004) provide a chronic RfD of 1.5 mg/kg-d for insoluble salts of Cr(III) based on an adjusted NOAEL of 1468 mg/kg-d from a chronic rat feeding study. An uncertainty factor of 100 is used to account for inter-species and human variability, and

a modifying factor of 10 is used for database deficiencies that reflect the fact that studies are needed in non-rodent mammals and that explicitly evaluate potential reproductive effects, and due to the concern raised around the potential for reproductive effects. The overall confidence in the RfD is reported to be low.

The ATSDR (2000) do not provide a minimal risk level (MRL) for reproductive and developmental effects from oral exposures to Cr(III) compounds, stating that the available data are either insufficient or too contradictory. However, they do provide a provisional guideline for Cr(III) and Cr(VI) based on the safe daily dietary intake of 0.003 mg/kg-day for a 70 kg individual (NRC 1989).

Health Canada (2003b) do not provide an oral TDI for Cr(III) compounds.

Total Chromium

Health Canada (2003b) provides an oral non-carcinogenic tolerable daily intake of 0.001 mg/kg-d for total chromium, based on the Canadian Guidelines for Drinking Water Quality listed in Health Canada (1986). The toxicological rationale for the selection of this TDI, including the endpoint, is not clear.

Cancer

Cr(VI) Compounds

The U.S. EPA (2004) state that the potential carcinogenicity of Cr(VI) compounds *via* oral exposure cannot be determined, and they could not locate studies that demonstrated that it was. A slope factor is not provided. The ATSDR (2000) does not provide cancer effect levels (CELs) for oral exposure to Cr(VI). Health Canada (2003b) does not provide oral slope factors for Cr(VI).

Cr(III) Compounds

The U.S. EPA (2004) have further concluded that ingestion of insoluble salts of Cr(III) is not classifiable as to human carcinogenicity (Group D), due to inadequate data demonstrating its potential carcinogenicity. They acknowledge that there is increased concern around the potential carcinogenicity of Cr(III) because Cr(VI) has been classified as a known human carcinogen (*via* inhalation).

The ATSDR (2000) do not provide CELs for oral exposure to Cr(III) compounds.

Health Canada (1994) conclude there are insufficient available data to assess the potential carcinogenicity of insoluble salts of Cr(III) in humans and as such classifies them under Group IV, "Unclassifiable with Respect to Carcinogenicity in Humans."

Total Chromium
No slope factors or CELs are provided for oral exposure to total chromium.

Table C3-1 Oral Exposure Limits for Total Chromium

Chromium Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Cr(VI) soluble salts	0.003 mg/kg-d	Chronic	None (rat)	U.S. EPA 2004
Cr(III) and Cr(VI)	0.003 mg/kg-d	Safe daily dietary intake		ATSDR 2000
Cr(III) insoluble salts	1.5 mg/kg-d	Chronic	None (rat)	U.S. EPA 2004
Total chromium	0.001 mg/kg-d	Chronic	Not readily available	Health Canada 2003b
Cancer Effects				
Cr(VI) compounds	N/A[1]	-	-	-
Cr(III) insoluble salts	N/A[1]	-	-	-
Total chromium	N/A[1]	-	-	-

Note: [1]Not applicable

C3.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C3-2.

Non-Cancer

Cr(VI) Compounds
The U.S. EPA (2004) cites uncertainty in the relevance of adverse effects noted following occupational studies to chromium acid mists and dissolved Cr(VI), to environmental exposures by the general population, which is thought to occur *via* Cr(VI) compounds found in dust. For this reason, the U.S. EPA provide two different reference concentrations (RfCs) for Cr(VI) compounds. They provide a chronic RfC of $8x10^{-6}$ mg/m^3 for chromium acid mists and dissolved Cr(VI) aerosols based on a subchronic occupational study for nasal septum atrophy. An adjusted LOAEL of 0.000714 mg/m^3 is used. An uncertainty factor of 3 is used to extrapolate from a subchronic to a chronic exposure limit, another factor of 3 to extrapolate from a LOAEL to a NOAEL, and an additional uncertainty factor is incorporated to account for human variability. The overall confidence in this RfC is reported to be low.

A chronic RfC of 0.0001 mg/m^3 is provided for Cr(VI) particulates based on a rat subchronic study for changes in lactate dehydrogenase in bronchioalveolar lavage fluid. This second RfC is based on a benchmark concentration approach that adjusts the benchmark dose (which is defined as "the lower 95% confidence limit of the dose corresponding to a 10% relative change in the endpoint compared to the control" U.S.

EPA 2004) for lactate dehydrogenase in bronchioalveolar lavage fluid by: multiplication by a factor that accounts for the different Cr(VI) compound dust deposition in rodent and human lungs and for pharmacokinetic differences between humans and the test species, and division by uncertainty factors of 3 to account for further pharmacokinetic differences between species, 3 to extrapolate from a subchronic to a chronic study, and 10 to account for human variability. The overall confidence in this RfC is reported to be medium.

The ATSDR (2000) provide a minimal risk level (MRL) of $5x10^{-6}$ mg/m^3 for inhalation exposures to Cr(VI) based on intermediate exposure to chromic acid mists and other dissolved hexavalent chromium aerosols and mists by occupationally-exposed workers. The toxicological endpoint is respiratory effects, which include nasal irritation, mucosal atrophy and ulceration, and decreases in spirometric parameters. The LOAEL value is adjusted for continuous exposure, and is divided by an uncertainty factor of 10 to account for human variability and an additional 10 to account for extrapolation from a LOAEL. The ATSDR (2000) provides a second MRL of 0.001 mg/m^3 for intermediate inhalation exposures to particulate Cr(VI) compounds by rats, which is calculated based on a benchmark dose approach. The toxicological endpoint is alterations in lactate dehydrogenase in bronchioalveolar lavage fluid. Uncertainty factors include division by a factor of 3 to account for extrapolation from animals to humans, and a factor of 10 for human variability.

Health Canada (2003b) do not provide a tolerable concentration for (non-cancer) inhalation exposures to Cr(VI).

Cr(III) Compounds

The U.S. EPA (2004) do not provide a reference concentration for insoluble salts of Cr(III), citing an inadequate database regarding the respiratory effects of Cr(III). The ATSDR do not provide MRLs for inhalation exposure to Cr(III) compounds. Health Canada (2003b) do not provide inhalation slope factors for Cr(III) compounds.

Total Chromium

No non-cancer exposure limits are provided for inhalation exposures to total chromium.

Cancer

Cr(VI) Compounds

The U.S. EPA (2004) provide an inhalation unit risk of 12 per (mg/m^3) for mortality resulting from lung cancer. The unit risk is based on occupational data that relate inhalation of chromium to lung cancer rates in exposed workers (Mancuso 1975). Although the workers were exposed to both Cr(III) and (VI) compounds, there are no data available on the carcinogenicity of Cr(III) and so the relationship between chromium exposure and lung cancer was estimated to be due to Cr(VI) compounds, which were assumed to make up no less than one-seventh of total chromium. The certainty that Cr(VI) compounds are carcinogenic *via* inhalation is due to consistent results produced by investigators for different occupational study populations, and because Cr(VI) has also been shown to be carcinogenic in animal studies. The relationship between exposure to chromium and occurrence of lung cancer is considered sufficient to derive a dose-response relationship. A multistage, extra risk extrapolation method is employed to derive the unit risk. The unit risk should not be used if the air concentration exceeds 0.0008 mg/m^3, since it may not be appropriate above this concentration.

The ATSDR (2000) provides cancer effect levels (CELs) for exposures to Cr(VI) compounds resulting in lung cancer, including a CEL of 0.5 mg/m^3 based on an occupational study for inhalation exposures to lead and zinc chromate (containing Cr(VI)) for 4-19 years. Another CEL of 0.25 mg/m^3 is based on an occupational study for inhalation exposures to soluble Cr(VI) for 1-7 years.

Health Canada (2003b) provide both an inhalation slope factor of 331 per (mg/kg-d) and an inhalation unit risk of 75.8 per (mg/m^3) for Cr(VI) compounds. Both are calculated from the tumourigenic concentration$_{0.05}$ ($TC_{0.05}$; in this case, the concentration that induces a 5% increase in mortality from lung cancer) from the occupational study conducted by Mancuso (1975).

Cr(III) Compounds

The U.S. EPA (2004) further conclude that ingestion of insoluble salts of Cr(III) is not classifiable as to human carcinogenicity (Group D), due to inadequate data demonstrating its potential carcinogenicity. They acknowledge that there is increased concern around the potential carcinogenicity of Cr(III) because Cr(VI) has been classified as a known human carcinogen (*via* inhalation).

The ATSDR (2000) provide cancer effect levels (CELs) for exposures to Cr(III) compounds resulting in lung cancer, including a CEL of 0.25 mg/m^3 based on an occupational study for inhalation exposures to insoluble Cr(III) for 1-7 years.

Health Canada (1994) conclude there are insufficient available data to assess the

potential carcinogenicity of Cr(III) compounds in humans, and as such has classified them under Group IV, "Unclassifiable with Respect to Carcinogenicity in Humans."

Total Chromium

Health Canada (2003b) provide both an inhalation slope factor of 47.6 per (mg/kg-d) and an inhalation unit risk of 10.9 per (mg/m^3) for total chromium. The toxicological rationale for the selection of this slope factor is not clear.

Table C3-2 Inhalation Exposure Limits for Total Chromium

Chromium Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Chromic acid mists and dissolved Cr(VI)	8×10^{-6} mg/m³	Chronic	Nasal septum atrophy (occupational)	U.S. EPA 2004
Cr(VI) particulates	0.0001 mg/m³	Chronic	Lactate dehydrogenase in bronchioalveolar fluid (rat)	U.S. EPA 2004
Chromic acid mists and dissolved Cr(VI) aerosols	5×10^{-6} mg/m³	Intermediate	Respiratory effects (occupational)	ATSDR 2000
Particulate Cr(VI) compounds	0.001 mg/m³	Intermediate	Lactate dehydrogenase in bronchioalveolar fluid (rat)	ATSDR 2000
Cr(III) compounds	--[1]	-	-	-
Total chromium	--[1]	-	-	-
Cancer Effects				
Chromium (VI)	12 per (mg/m³)	Chronic	Mortality from lung cancer (occupational)	U.S. EPA 2004
Lead and zinc chromate	0.5 mg/m³	Chronic (Cancer effect level)	Lung cancer (occupational)	ATSDR 2000
Soluble chromium (VI)	0.25 mg/m³	Chronic (Cancer effect level)	Lung cancer (occupational)	ATSDR 2000
Chromium (VI)	75.8 per (mg/m³) or 331 per (mg/kg-d)	Chronic	Mortality from lung cancer (occupational)	Health Canada 2003b
Insoluble Cr(III)	0.25 mg/m³	Chronic (Cancer effect level)	Lung cancer (occupational)	ATSDR 2000
Total chromium	10.9 per (mg/m³) or 47.6 per (mg/kg-d)	Chronic	Not readily available	Health Canada 2003b

Note: [1] No data

C3.3.3 Selected Exposure Limits

Table C3-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C3-3 Selected Exposure Limits for Total Chromium for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Chromium (total)	oral	non-carcinogenic	0.003	mg/kg/d	No effect (oral exposure to chromium VI, rat study)	U.S. EPA 2004
	inhalation	carcinogenic	47.6	$(mg/kg/d)^{-1}$	Lung cancer (inhalation, human occupational exposure)	Health Canada 2003b

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C4.0 Toxicological Profile for Lead

Lead (Pb) is a bluish or silvery grey metal that is naturally occurring in the earth's crust, and can be extracted from minerals, rock and sediment. Lead is more frequently found in its (+2) oxidation state than in its (+4) oxidation state. Lead tends to form compounds with other chemicals, and can also form salts. Lead can form stable organic compounds such as tetraethyl lead and tetramethyl lead, which typically are found as colourless liquids with a high boiling point. Lead compounds can have different solubilities in water. For example, some lead salts such as lead nitrate and lead chlorate are soluble, while most other lead salts and metallic lead are not (ATSDR 1999).

Lead is released into the environment through many anthropogenic activities. At a global scale, the main source of lead emitted into air is the combustion of leaded motor fuels. Leaded motor fuels contain alkyl (organic) lead compounds that are used to increase octane rating. The widespread use of leaded motor fuels resulted in its ubiquitous distribution throughout the environment, and the use of lead as a fuel additive has now been banned in most industrialized countries. Environmental levels of lead have subsequently fallen since the banning of leaded fuel, although historical lead concentrations in soil can be significant (WHO 2000).

The smelting of lead ore and lead from scrap metal and batteries are another source of lead emissions to the environment. Moreover, because lead is found in the earth's crust, the smelting of copper, the production of iron and as well as coal combustion result in some lead emissions. Lead is used in the refining and manufacture of lead-containing compounds and products such as lead acid storage batteries, ammunition, sheet lead, solder, some brass and bronze products, pipes and ceramic glazes. Recent efforts have been made to decrease the lead content in paint, ceramic products, caulking, gasoline and solder due to concern over its health effects. Lead is used in medical equipment (for e.g., radiation shields), scientific equipment, and military equipment, and is also released during waste incineration and disposal processes (ATSDR 1999).

Drinking water distribution systems in homes containing lead pipes, PVC pipes, lead plumbing fittings and lead solder may be an important source of lead exposure for residents due to lead dissolution, especially in areas with soft or acidic water (WHO 1996).

Exposure pathways for lead typically include air, drinking water, food, soil and household dust *via* inhalation, ingestion and dermal exposure routes. Exposure pathways including the ingestion of food, soil and dust are likely to be the major source

of intake. Lead levels may be elevated in produce due to atmospheric deposition of lead and lead uptake from soil. Higher levels of lead are found in soil and in produce grown closer to combustion sources, such as near roads and in cities. Peeling paint and the dust generated from paint chips can also contain lead, and this is especially of concern in and around old buildings.

C4.1 Pharmacokinetics

The absorption of lead *via* oral exposure varies for adults and children, with adults absorbing about 10% of lead from food and children absorbing about 30% of lead from soil and dust (WHO 1996). Children appear to absorb more lead through oral exposure than adults; children absorb 30-50% of lead through the gastrointestinal (GI) tract (Ziegler *et al.* 1978, Alexander *et al.* 1974), while adults absorb 20-70% of water-soluble lead compounds in the GI tract when they are fasted. Adults who did not fast had lower absorption rates of 3-15% (James *et al.* 1985, Blake *et al.* 1983, Heard and Chamberlain 1983, Rabinowitz *et al.* 1980).

Physiological factors such as age, iron, calcium and potassium levels, nutritional status and pregnancy, as well as the physical-chemical properties of the ingested media determine the absorption of lead in the GI tract (ATSDR 1999). Absorption of lead in the gastrointestinal (GI) tract can increase if nutritional status is compromised and levels of iron, calcium or phosphorus are deficient (WHO 1996). Furthermore, meals containing calcium and phosphorus can lead to lower lead absorption. Pregnancy may lead to a higher absorption of lead. The particle size of lead compounds has been shown to affect the absorption of lead in the GI tract, with smaller particles experiencing a greater absorption than larger particles (ATSDR 1999).

Children with iron deficiencies were shown to have higher blood lead concentrations than similarly exposed children who were not iron-deficient. This is thought to result from either higher absorption of lead in the iron deficient children, or changes in lead biokinetics following ingestion. A similar phenomenon is observed in calcium deficient children and adults; a lower calcium intake results in higher lead absorption from the GI tract (ATSDR 1999).

The absorption of inorganic and organic lead can differ. The absorption of inhaled inorganic lead is related to how much particulate matter containing lead can reach the lungs, and this depends on particle size and ventilation rate. It is estimated that about 30-50% of particulate matter containing lead is deposited in the lungs, and absorption of deposited lead is almost 100% in adults. Absorption rates for inhaled lead in children are not known. The absorption of inhaled organic lead compounds is similarly high; although a large extent of some of the volatile organic leaded compounds were exhaled in humans (ATSDR 1999).

Lead is able to pass through the placental barrier, and fetal blood lead levels were measured to be about 80% to 100% of those of maternal blood (Angell and Lavery 1982; Gershanik *et al.* 1974). Studies from adults and from rats suggest that lead in soils is absorbed to a lesser extent than dissolved lead in the GI tract. Lead in soil is absorbed to an even lesser extent when soil is ingested following a meal (ATSDR 1999). There are no data on lead absorption from soil in children.

It is suspected that absorption of lead and lead intake may have a curvilinear relationship, but this has not been proven. It is speculated that the relationship may be linear at low doses, but that absorption may decrease at high doses of lead. The mechanism by which this would occur is unclear, but is thought to be some kind of capacity limited process such as saturation of available transport pathways into cells (ATSDR 1999).

There is limited information available on the dermal absorption of lead. However, dermal absorption of inorganic lead is thought to be much less than absorption following oral or inhalation exposures. Dermal absorption of organic lead compounds may be greater. For example, studies performed in rabbits and in rats showed a high and fast absorption of tetraethyl lead compounds through the skin (Laug and Kunze 1948, Kehoe and Thamann 1931).

The distribution and metabolism of inorganic and organic lead in the body appears to be the same. Following absorption, binding to hemoglobin in the blood allows lead to travel rapidly and widely throughout the body. Lead is then distributed to the soft tissues, including the blood, liver, lung, spleen, kidney and bone marrow, and in the long term, gets redistributed to the skeleton. Lead distributed to the soft tissues usually undergoes a rapid turnover rate, while lead distributed to the skeleton usually undergoes a slow turnover rate (Health Canada 1992). Lead accumulates more in the bones of adults than the bones of children; the relative accumulation rates are from 80-95% for adults and 72% for children (Alessio and Foa 1983; Barry 1978). Lead accumulates more in areas of bone that are undergoing active calcification when the individual is exposed, and these areas will differ for children and adults (ATSDR 1999). Biological half-lives for lead in the blood and in bone are 16 to 40 days and 17 to 27 years, respectively (Holtzman 1978, Rabinowitz *et al.* 1976, Chamberlain *et al.* 1975).
Inorganic lead is not metabolized in the body, but it is able to form complexes with proteins and non-protein compounds. The absorption, distribution and excretion of inorganic lead can occur when it exists as a compound (ATSDR 1999). On the other hand, some organic lead compounds such as alkyl lead compounds are metabolized in the liver by cytochrome P-450. Cytochrome P-450 has been shown to catalyze the dealkylation reaction of alkyl lead compounds in rabbits, dogs and mice.

Elimination of lead occurs primarily *via* the feces for lead that was unabsorbed in the GI tract. A secondary route of elimination for unabsorbed GI lead is through biliary clearance into the GI tract. Absorbed lead is mostly excreted in the urine.

C4.2 Toxicology

The mechanisms of lead toxicity arise from its ability to mimic or inhibit the action of calcium in the body, and from its ability to interact with proteins (Goering 1993, Goldstein 1993, Goyer 1993, Fowler 1992, Bressler and Goldstein 1991). Lead can mimic calcium's activation of calmodulin by binding to hydroxyl groups, and can mimic the activation of protein kinase C by binding to sulfhydryl groups. Calmodulin and protein kinase C are both involved in cellular calcium metabolism, and binding of lead is thought to increase cellular reactivity and possibly result in hypertension. Protein kinase C is also involved in cell growth and differentiation. Lead can interfere with the active metabolite of vitamin D, 1,25-dihydroxy-vitamin D and disrupt signaling pathways and calcium homeostasis. Lead interacts with proteins by binding to sulfhydryl, amine, phosphate and carboxyl groups. Lead can also inhibit synaptic transmission by blocking calcium channels in neurons (ATSDR 1999).

C4.2.1 Non-Cancer Effects

The most sensitive target organs for lead are thought to be the nervous system, the hematopoetic system, and the cardiovascular system. Toxic effects of lead are also manifested through the kidneys, immunological and reproductive systems (ATSDR 1999).

Nervous system effects of acute lead exposures *via* oral and inhalation routes include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, hallucinations and loss of memory. Encephalopathy may also result at high lead exposure levels in both adults and children (Health Canada 1992).

Chronic exposure to lead in adults has been reported to result in effects such as tiredness, sleeplessness, irritability, headaches, joint pain and GI symptoms at blood lead levels of 50-80 µg/dL. Further symptoms, including muscle weakness, gastrointestinal symptoms, lower scores on psychometric tests, disturbances in mood and peripheral neuropathy were reported following occupational exposures of 1 to 2 years in workers whose blood levels ranged from 40 to 60 µg/dL. Nerve conduction velocities were reduced at blood levels of 30 to 50 µg/dL (Health Canada 1992).

Nervous system effects of lead toxicity can occur both in the central and peripheral nervous systems, and are thought to be the main targets for lead toxicity. Specific symptoms resulting from exposure below 30 µg/dL include neurological and

behavioural effects in adults, and electrophysiological evidence of central and peripheral nervous system effects in children. A number of cross-sectional epidemiological studies conducted in children have demonstrated a statistically significant relationship between blood lead levels of 30 ug/dL of more and reductions in IQ of about 4 points. Reductions in IQ have been shown to be associated with lower blood levels, but these relationships were not statistically significant. Moroever, these studies and longitudinal epidemiological studies on infants and children designed to assess the effects of low levels of blood lead on cognitive development suggest that it is difficult to determine a threshold under which adverse neurological effects in children or adverse effects on child development do not occur (ATSDR 1999).

Chronic exposure to lead can also lead to nephropathy in adults and children, but has not been detected at blood levels below 40 µg/dL (Health Canada 1992). An epidemiological study suggested that at blood lead levels greater than 37 µg/dL, lead-induced renal effects resulting in hypertension might occur (Pocock *et al.* 1984). Further, a US National Health and Nutrition Examination Survey (NHANES II) determined an association between high diastolic blood pressure in people ages 21-55 and blood lead levels from 7-34 ug/dL (Harlan *et al.* 1985; Pirkle *et al.* 1985), although the reliability of this study is not clear (WHO 1996).

The hematopoetic effects of lead toxicity occur as a result of lead's interference with enzymes involved in the formation of haem, the oxygen-carrying component of red blood cells. The only well-defined hematopoetic effect of lead is anemia, which has been observed in patients with blood levels greater than 40 µg/dL. Inhibition of d-aminolevulinic acid dehydrase has been observed in children with much lower blood levels, but these were not associated with any adverse effect (Health Canada 1992).

The reproductive effects of lead include gonadal dysfunction in men with blood lead levels of 40 to 50 µg/dL and reproductive dysfunction has not been ruled out in females exposed to lead. Female workers occupationally exposed to lead have experienced increases in spontaneous abortion and stillbirths. Lower levels of lead typical of environmental exposures have been associated with higher miscarriage, stillbirth and pre-term delivery rates. Rodent data support human findings that lead exposure may result in reproductive effects in both males and females (Health Canada 1992).

C4.2.2 Cancer Effects

Occupational studies have assessed the carcinogenicity potential of lead, and results are inconclusive. One small study did find a significant increase in deaths from chronic renal disease, consistent with results from rodent studies showing the generation of renal tumours following acute oral doses of lead salts in food, and from chronic exposure to lead *via* the diet. Another occupational study of battery factory and smelter workers showed a slight excess of deaths from digestive and respiratory system

cancers. A follow-up study on battery factory workers reported an excess of deaths from respiratory cancer, but these results are equivocal given that smoking was not accounted for as a possible confounding factor.

The International Agency for Research on Cancer (IARC) has determined that lead is a possible human carcinogen (Group 2B), based on inadequate evidence in humans but sufficient evidence in animals. The U.S. EPA classify inorganic lead as a possible human carcinogen (Group B2). Health Canada (1992) classify lead as possibly carcinogenic to humans (Group IIIB), stating inadequate human data and limited evidence of carcinogenicity in animals.

C4.2.3 Susceptible Populations

Sub-populations that may be particularly susceptible to adverse health effects from lead exposure include infants and children up to the age of six, pregnant women and the developing fetus, the elderly, smokers, alcoholics, individuals with genetic diseases that have an impact on haem synthesis, and individuals with inadequate nutrition, or with kidney or neurological dysfunction (ATSDR 1999, Health Canada 1992).

Children are more at risk due to their greater GI absorption of lead *via* oral exposure, because they ingest more soil and dust as a result of hand-to-mouth behaviour or pica, because there is a higher likelihood they have a nutritional deficiency of zinc, calcium or iron, because they may have a lower threshold for certain adverse effects of lead, and because some of the health effects resulting from lead exposure may be more severe in children than in adults. Furthermore, children living in urbanized and low-income areas of the city may be at greater risk of health effects from lead due to higher soil lead concentrations and possibly due to exposure to dust and paint chips from the leaded paint common in old buildings. Infants are also exposed to lead through breast milk, and the developing embryo and fetus are exposed to lead through maternal transfer *via* the placenta (ATSDR 1999).

Periods of higher bone demineralization such as those that occur during pregnancy, lactation and osteoporosis may mobilize lead bound to bone into the blood. For this reason, pregnant women and the elderly may be at greater risk of experiencing the adverse effects of lead. Individuals with genetic diseases that impact haem synthesis, such as thalassemia, may also be at greater risk. Further genetic diseases thought to present a greater risk for the toxic effects of lead include children with sickle cell disease, individuals with porphyrias, and genetic diseases that cause excessive δ-aminolevulinic acid (ALA) synthetase activity.

C4.3 Current Exposure Limits

C4.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C4-1.

Non-Cancer

The U.S. EPA (2004) do not provide a reference dose (RfD) for inorganic lead or lead compounds because they consider that it would be inappropriate to do so. They state that some of lead's adverse health effects, namely changes in blood enzyme levels and effects on neurobehavioural development in children, may be non-threshold effects, meaning even a very small dose could be associated with a significant effect in some individuals. Moreover, they state that determining an appropriate risk value using a typical approach may not be accurate because individuals have different pre-existing body burdens that are affected by factors including age, nutritional and health status and pregnancy. These factors would all impact the toxicokinetics of lead.

The U.S. EPA (2004) provide a RfD of $1x10^{-7}$ mg/kg-d for oral exposure to tetraethyl lead. The RfD is based on a LOAEL of 0.0012 mg/kg-d, derived from a subchronic rat study that involved administration of tetraethyl lead in peanut oil by gavage. The endpoint is histopathology of liver and thymus. An uncertainty factor of 10,000 is used: 10 to account for inter-species differences, 10 to account for human variability, 10 to convert a subchronic to a chronic study, and 10 for the use of a LOAEL for the derivation of the RfD. The overall confidence in the RfD is reported to be medium.

The ATSDR (1999) do not provide minimal risk levels (MRLs) for lead, stating the lack of a clear threshold of toxicity for lead, the need to examine multiple routes of exposure for lead, different absorptions of lead compounds, and the effects of nutrition and age on absorption as complications rendering the determination difficult.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable weekly intake (pTWI) of 0.025 mg/kg in 1986 for lead exposure to children, and reconfirmed this value in 1993 while broadening it to encompass all age groups (WHO 1996). This is equivalent to an RfD (or tolerable daily intake, TDI) of 0.0035 mg/kg-d. This exposure limit is prescribed based on the knowledge that lead is a cumulative toxin and that any increase in lead body burdens should be avoided. The NOAEL of 0.003 to 0.004 mg/kg-d is taken from metabolic studies in infants, and was not associated with any increases in blood lead levels or lead body burdens. A LOAEL of 0.005 mg/kg-d was identified to be associated with body retention of lead. An uncertainty factor of 2 was selected because the endpoint and receptor selected were conservative, and because the studies selected were of good quality.

Health Canada (1992) endorse the JECFA pTWI, and Health Canada (2003) provide a very similar oral TDI of 0.0036 mg/kg-d. However, the toxicological rationale and endpoint are not explicitly stated in Health Canada (2003).

Cancer

The U.S. EPA (2004) classify inorganic lead as a probable human carcinogen (Group B2) based on rodent evidence showing significant increases in renal tumours in animals exposed orally and subcutaneously to soluble lead salts. However, human data is deemed inadequate and no slope factor is provided for inorganic lead or lead compounds. Moreover, they state that determining an appropriate risk value using a typical approach may not be accurate because individuals have different pre-existing body burdens that are affected by factors including age, nutritional and health status and pregnancy. These factors would all impact the toxicokinetics of lead.

The ATSDR (1999) provide cancer effect levels (CELs) ranging from 27 mg/kg-d to 371 mg/kg-d for renal tubular adenomas and carcinomas resulting from chronic rodent exposure to lead acetate in food and drinking water. Exposure durations ranged from 76 weeks to 2 years.

Health Canada (2003, 1996) do not provide any slope factors or unit risks for lead.

Table C4-1 Oral Exposure Limits for Lead Compounds

Lead Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Tetraethyl Lead	$1x10^{-7}$ mg/kg-d	Chronic	Histopathology of liver and thymus	U.S. EPA 2004
Lead	0.0035 mg/kg-d	Chronic	Increases in blood lead levels or in lead retention	JECFA 1993, in WHO 1996
Lead	0.0036 mg/kg-d	Chronic	Not readily available	Health Canada 2003
Cancer Effects				
Lead acetate	27 - 371 mg/kg-d	Chronic	Renal cancer (Cancer Effect Levels, CELs)	ATSDR 1999

C4.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C4-2.

Non-Cancer

The ATSDR (1999) do not provide minimal risk levels (MRLs) for lead, stating the lack of a clear threshold of toxicity for lead, the need to examine multiple routes of exposure for lead, different absorptions of lead compounds, and the effects of nutrition and age on absorption as complications rendering the determination difficult.

The U.S. EPA and Health Canada do not provide exposure limits for non-cancer health effects resulting from inhalation exposure to arsenic.

The WHO (2000) determined an air unit risk of 0.0005 mg/m^3 for lead. This was derived from a LOAEL of 100 µg/L lead in blood for a toxicological endpoint of cognitive deficit, hearing impairment, and altered vitamin D metabolism in children.

Cancer

The ATSDR (1999) does not provide CELs for lead.

The U.S. EPA (2004) and Health Canada (2003, 1996) do not provide an inhalation slope factor for inorganic lead or lead compounds.

Table C4-2 Inhalation Exposure Limits for Lead Compounds

Lead Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Lead	0.0005 mg/m^3	Chronic	Cognitive deficit, hearing impairment, altered vitamin D metabolism	WHO 2000
Cancer Effects				
Lead	--[1]	-	-	-

Note: --[1] No data

C4.3.3 Selected Exposure Limits

Table C4-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C4-3 Selected Exposure Limits for Lead Compounds for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Lead	oral	non-carcinogenic	0.0036	mg/kg/d	Although not explicitly stated it is likely that the value is based on increases in blood lead levels or in lead retention as it is similar to the WHO (1996) value	Health Canada 2003

C4.4 References

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C5.0 Toxicological Profile for Mercury

Mercury occurs naturally in the environment and exists in several forms. These forms can be organized into three categories: metallic mercury, inorganic mercury, and organic mercury.

Metallic mercury is a shiny, silver-white metal that is a liquid at room temperature. Metallic mercury is the elemental or pure form of mercury (i.e., it is not combined with other elements). At room temperature, some of the metallic mercury will evaporate and form mercury vapors. Some uses of metallic mercury are production of chlorine gas, extracting gold from ore, thermometers, batteries and dental filling.

Inorganic mercury compounds occur when mercury combines with elements such as chlorine, sulfur, or oxygen. Some inorganic mercury compounds are used as fungicides. Mercuric chloride can be used as a topical antiseptic or disinfectant agent. Mercuric sulfide and mercuric oxide may be used to color paints and tattoo dyes.

When mercury combines with carbon, the compounds formed are called "organic" mercury compounds or organomercurials. The most common organic mercury compound is methylmercury. Methylmercury is produced primarily by microorganisms (bacteria and fungi) in the environment, rather than by human activity. Methylmercury is of particular concern because it can build up in certain edible freshwater and saltwater fish and marine mammals to levels that are many times greater than levels in the surrounding water.

C5.1 Pharmacokinetics

Inhaled metallic mercury is quickly absorbed through the lungs into the blood, and 70–80% is retained. Absorption of liquid metallic mercury following oral exposure is negligible (<0.01%) (Health Canada 1979). Absorption of ingested inorganic mercuric salts may range from 2% to 38% depending upon the form and conditions. Oral absorption of organic mercury is nearly complete, but respiratory absorption data are lacking, particularly for the alkyl mercurials (ATSDR 1999). All mercuric compounds are known to be dermally absorbed to some extent, but rates have not been measured (Health Canada 1979).

The distribution data for metallic, inorganic, and organic mercury are consistent in identifying the kidney as the organ with the highest mercury bioaccumulation. Kidneys contain the detoxifying metal-binding protein, metallothionein, and mercury accumulation results in higher production of metallothionein in the kidney. Because of

its high lipophilicity (preference for fatty tissues), metallic mercury can also be transferred readily through the placenta and blood-brain barrier. The oxidation of metallic mercury to the inorganic divalent cation in the brain can result in retention in the brain. Inorganic mercury compounds can reach most organs; however, their low lipophilicity reduces their ability to penetrate barriers and to accumulate in the brain and fetus. The distribution of methylmercury is similar to that of metallic mercury; a relatively large amount of mercury can accumulate in the brain and fetus (compared to inorganic mercury) following its conversion to the inorganic divalent cation, while large amounts are distributed to the kidney and to a lesser extent, the liver. In blood, methylmercury binds to red blood cells. Since there is a direct relationship, levels in hair can be used to assess exposures (Health Canada 1979). Hair levels can also be used to assess exposure to inorganic mercury.

All mercuric compounds are linked to oxidation-reduction cycles following absorption. Metallic mercury in red blood cells can be oxidized to inorganic divalent mercury by the hydrogen peroxidase-catalase pathway, while oxidation can also occur in the brain, liver and other tissues (Clarkson 1989; Halbach and Clarkson 1978). Inorganic mercury may be reduced to metallic mercury following its absorption and oxidation, while organic mercury may be converted to inorganic divalent cation following absorption.

Mercuric compounds undergo excretion through different pathways in humans. Organic mercury is excreted primarily *via* the bile, followed by the faeces and urine, and to a lesser extent *via* the hair and lungs. Metallic mercury is excreted *via* the urine, faeces and lungs, while inorganic mercury is excreted mainly through faeces and to a lesser extent urine. Animal data suggest that mercury excretion in humans may be age-dependent. Organic and inorganic mercury may be excreted in breast milk. The biological half-life of metallic mercury in humans is approximately 60 days, while the average biological half-life of methylmercury in hair and blood ranged from 45-70 days (ATSDR 1999).

C5.2 Toxicology

The toxicity of mercuric compounds is related to the ability of the inorganic divalent cation to bind to protein sulfhydryl, thiol, amine and carboxyl groups, which may result in protein inactivation, affect protein transport, as well as disrupt functioning of the cell membrane and other cellular structures.

C5.2.1 Non-Cancer Effects

Inhalation Exposure

The documented effects of mercury exposures through inhalation mostly relate to metallic mercury vapor, and other forms of inorganic mercury do not pose a risk by the inhalation pathway. In humans, respiratory effects are a prominent effect of acute-duration high-level exposure to metallic mercury vapors, while cardiovascular, gastrointestinal (GI) and hematological effects have also been reported. Symptoms of inhalation exposures to metallic mercury vapor may include cough, dyspnea, tightness or burning pains in the chest, fatigue, fever, chills, elevated leukocyte count, behavioural and motor disturbances. Inhalation of sufficient levels of metallic mercury vapor has been associated with systemic toxicity in both humans and animals. The most sensitive target organs of metallic mercury-induced toxicity are the kidneys and the central nervous system. In both humans and animals, acute inhalation exposures to inorganic mercury have been shown to result in respiratory, cardiovascular and GI effects. Inhalation of organic mercury vapor has been reported to result in neurological, GI, renal and muscular effects, as well as death. Acute and chronic exposure to mercuric compounds also result in musculoskeletal effects such as tremors and muscle pain, but these are suspected of being secondary to the neurological effects produced. (ATSDR 1999)

Oral Exposure

Acute oral exposures of all mercuric compounds generally result in shock, cardiovascular shock, acute renal failure, and severe GI damage. Acute oral exposures of inorganic mercury salts in both humans and animals can result in both renal and GI effects. Acute symptoms can include pharyngitis, disphagia, abdominal pain, nausea and vomiting, bloody diarrhea and shock.

Chronic oral exposure to inorganic mercury compounds has resulted in systemic poisoning, GI and renal effects, and dementia. Oral exposure to even minute quantities of organic mercury compounds have been reported to cause severe effects such as death and neurological effects, and symptoms may manifest weeks and months following exposure (Health Canada 1979).

In animals, subacute exposures have been shown to result in renal and liver effects, but neurological effects were not noted. More acute exposures in animals (and humans) have resulted in effects on the central nervous system.
Probably the most widely recognized form of hypersensitivity to mercury poisoning in humans is the uncommon syndrome known as acrodynia, also called erythredema polyneuropathy or pink disease (ATSDR 1999).

The most sensitive adverse effect for mercury risk assessment is formation of mercuric-mercury-induced autoimmune glomerulonephritis. The production and deposition of IgG

antibodies to the glomerular basement membrane can be considered the first step in the formation of this mercuric-mercury-induced autoimmune glomerulonephritis.

C5.2.2 Cancer Effects

The U.S. EPA (2004) consider metallic mercury to be not classifiable as to human carcinogenicity because there are inadequate human and animal data. Epidemiological studies did not show a correlation between inhalation exposure and carcinogenicity, although there were study confounders. Genotoxicity test results for metallic mercury are inconclusive.

The U.S. EPA (2004) consider inorganic mercury a possible human carcinogen because there is limited evidence of carcinogenicity in rats and mice, and no data in humans. Oral carcinogenicity studies in rats and mice demonstrated some occurrences of GI and thyroid tumours following chronic exposure to mercuric chloride. Furthermore, genotoxicity assays of mercuric chloride showed mixed results.

The U.S. EPA (2004) consider methylmercury a possible human carcinogen due to inadequate data in humans and because there is limited carcinogenicity in animals. Mice that were orally exposed to methylmercuric chloride showed higher incidence of renal tumours and nephrotoxicity. Genotoxicity data on methylmercury are inconclusive.

C5.2.3 Susceptible Human Populations

Populations will be more susceptible to displaying an altered response to mercury due to genetic makeup, developmental stage, age, health and nutritional status and substance exposure history. This is because these factors may result in the decreased function of detoxification and excretory processes and target organs. Compared to a healthy young adult, populations particularly sensitive to mercury toxicity include the elderly, people with pre-existing disease, and young infants and children who are still developing (ATSDR 1999).

C5.3 Current Exposure Limits

C5.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C5-1.

Non-Cancer

Metallic Mercury

The U.S. EPA (2004) and Health Canada (2003) do not provide any oral exposure limits. ATSDR (1999) do not provide any oral exposure limits due to absence of data, but they speculate that small quantities of liquid mercury are not expected to pose a health risk due to the poor intestinal absorption of metallic mercury.

Inorganic Mercury

The U.S. EPA (2004) provide a reference dose (RfD) of 0.0003 mg/kg-d. This value is based on a review of studies of subchronic feeding and subcutaneous exposure of mercuric chloride to rats. The critical effect is autoimmune effects. A LOAEL 0.226 mg/kg-d was determined (Druet *et al.* 1978). The RfD is derived by dividing the LOAEL by an uncertainty factor (UF) of 1000: 10 for extrapolation of a NOAEL to a LOAEL, 10 for the use of subchronic studies and a 10 for interspecies and human variability. The overall confidence in the RfD is reported to be high.

ATSDR (1999) developed an acute exposure MRL of 0.007 mg/kg-d. The MRL was based on a NOAEL of 0.93 mg/kg-d for renal effects in rats administered mercuric chloride 5 days a week for 2 weeks. An intermediate-duration MRL of 0.002 mg/kg-d has been derived based on a NOAEL of 0.23 mg/kg-d for renal effects in rats administered mercuric chloride 5 days a week for 6 months. Renal toxicity is a sensitive acute and chronic end point for inorganic mercury toxicity, as seen in other animal studies as well as in human case reports (ATSDR 1999). No chronic MRL was reported.

Health Canada (2003) provide a Tolerable Daily Intake (TDI) of 0.0003 mg/kg-d. Examination of the supporting documentation (CCME 1999) shows that the value from the U.S. EPA IRIS has been adopted.

Organic Mercury

The U.S. EPA (2004) provide a chronic RfD of 0.0001 mg/kg-d for methylmercury. This value is based on a benchmark dose approach for neurological effects from three human epidemiological studies that took place on the Faroe Islands (Grandjean *et al.*, 1997), in New Zealand (Kjellstrom *et al.*, 1989, 1986) and the Seychelles Islands

(Myers *et al.*, 1997, 1995a-c; Davidson *et al.*, 1998, 1995). The critical effect was developmental neuropsychological impairment in the offspring at age seven. Daily dietary intake levels of the mothers were used as a dose surrogate for the observed developmental effects for the fetus. The mother's dietary intake rates were derived using measured blood concentrations together with hair concentrations. An uncertainty factor of 10 was incorporated into the RfD to account for interindividual toxicokinetic variability in ingested dose estimation and pharmacodynamic variability and uncertainty. The overall confidence in the RfD was reported to be high.

No MRLs were derived for acute or intermediate oral exposure to organic mercury compounds due to the absence of data or to the lack of sufficient information regarding exposure levels associated with the reported observed effects (ATSDR 1999). A chronic-duration MRL of 0.0003 mg/kg-d for methylmercury was derived based upon the Seychelles Child Development Study (SCDS), in which over 700 mother-infant pairs were followed and tested from birth through 66 months of age (Davidson *et al.* 1998). The critical endpoints were neurobehavioural and developmental effects that were used to test for neurotoxicity. Levels of mercury in maternal hair were measured and used to assess fetal exposure. Results showed no occurrence of adverse effects resulting from chronic ingestion of low levels of methylmercury in fish. The MRL is calculated from the NOAEL of 15.3 mg/kg in maternal hair that was determined from the Davidson *et al.* (1998) study.

Health Canada (1979) provide an oral TDI of 0.03 mg/d for methylmercury for a 70-kg adult using a safety factor of 10, citing epidemiological studies demonstrating irreversible neurological symptoms in the derivation of drinking water guidelines. This TDI can be re-calculated as 0.00043 mg/kg-d.

Cancer

Metallic Mercury

The U.S. EPA (2004) have deemed that metallic mercury is not classifiable as to human carcinogenicity (Group D). No slope factor is provided.

Inorganic Mercury

The U.S. EPA (2004) have deemed that mercuric chloride is a possible human carcinogen (Group C). No slope factor is provided. ATSDR (1999) provide a cancer effect level (CEL) of 3.7 mg/kg-d for oral exposure. This CEL is based on a rat study that showed increased incidence of GI and thyroid tumours from exposure to mercuric chloride for 2 years at a dose rate of 5 days per week.

Organic Mercury

The U.S. EPA (2004) have deemed that methylmercury is a possible human carcinogen (Group C). No slope factor is provided. ATSDR (1999) do not provide exposure limits

for carcinogenicity via oral exposure due to lack of data, although they note several rodent studies which suggest that organic mercury compounds other than methylmercury have been associated with increases in renal tumours.

Table C5-1 Oral Exposure Limits for Mercury Compounds

Mercury Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Metallic Mercury	N/A[1]	-	-	-
Inorganic Mercury: Mercuric Chloride	0.0003 mg/kg-d	Subchronic	Autoimmune effects (rat; feeding and subcutaneous exposure)	U.S.EPA 2004
	0.007 mg/kg-d	Acute	Renal effects (rat)	ATSDR 1999
	0.002 mg/kg-d	Intermediate	Renal effects (rat)	ATSDR 1999
	0.0003 mg/kg-d	Same as U.S. EPA 2004	Same as U.S. EPA 2004	Health Canada 2003
Organic Mercury: Methylmercury	0.0001 mg/kg-d	Chronic	Neurological effects (epidemiological)	U.S.EPA 2004
	0.0003 mg/kg-d	Chronic	Neurobehavioural and developmental effects (epidemiological)	ATSDR 1999
	0.00043 mg/kg-d	Chronic	Irreversible neurological symptoms (epidemiological)	Health Canada 1979
Cancer Effects				
Metallic Mercury	N/A[1]	-	-	-
Inorganic Mercury: Mercuric Chloride	3.7 mg/kg-d	Chronic	GI and thyroid tumours (rat)	ATSDR 1999
Organic Mercury: Methylmercury	N/A[1]	-	-	

Note: [1]Not applicable

C5.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C5-2.

Non-Cancer

Metallic Mercury

U.S. EPA (2004) provide a reference concentration (RfC) of 0.0003 mg/m^3 for chronic inhalation occupational exposure. Workers exposed to low levels of mercury vapour for an average of 15.3 years experienced a significant increase in the velocity of intention

tremors (Fawer *et al.* 1983). These findings are consistent with neurophysiological impairments that might result from accumulation of mercury in the cerebellum and basal ganglia. A converted LOAEL of 0.009 mg/m^3 was determined, and the RfD was derived by dividing the LOAEL by an uncertainty factor of 30: 10 to account for human variability, and 3 was used for lack of data, particularly from developmental and reproductive studies. The overall confidence in the RfC is reported to be medium.

ATSDR (1999) provide a chronic-duration MRL of 0.0002 mg/m^3 for chronic inhalation occupational exposure. Workers exposed to low levels of mercury vapour for an average of 15.3 years experienced a significant increase in the velocity of intention tremors (Fawer *et al.* 1983). ATSDR (1999) argue that this MRL may also be sufficiently protective of neurodevelopmental effects in developing embryos/fetuses and children, who are considered the most sensitive subpopulations in terms of toxicity from metallic mercury. A LOAEL of 0.0062 mg/m^3 was determined, and the RfD was derived by dividing the LOAEL by an uncertainty factor of 30: 10 to account for human variability and 3 because the LOAEL used was considered of minimal-effect.

Inorganic Mercury

The U.S. EPA (2004), ATSDR (1999) and Health Canada (2003) do not provide any inhalation exposure limits due to absence of data.

Organic Mercury

The U.S. EPA (2004), ATSDR (1999) and Health Canada do not provide any inhalation exposure limits.

Cancer

Metallic Mercury

The U.S. EPA (2004) has deemed that metallic mercury is not classifiable as to human carcinogenicity (Group D). No slope factor is provided. ATSDR (1999) do not provide a carcinogenicity exposure limit, although they mention several epidemiological studies that have failed to show a correlation between metallic mercury inhalation exposure and cancer.

Inorganic Mercury

The U.S. EPA (2004) have deemed that mercuric chloride is a possible human carcinogen (Group C). No slope factor is provided. ATSDR (1999) does not address carcinogenicity exposure limits for inhalation exposure to inorganic mercury.

Organic Mercury

The U.S. EPA (2004) has deemed that methylmercury is a possible human carcinogen (Group C). No slope factor is provided. ATSDR (1999) do not provide a carcinogenicity exposure limit, although they list a study that suggested there is an

association between organic mercury containing products and leukemia in humans and cattle, but study confounders were present.

Table C5-2 Inhalation Exposure Limits for Mercury Compounds

Mercury Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Metallic Mercury	0.0003 mg/m^3 or 8.6x10^{-5} mg/kg-d	Chronic	Neurophysiological effects (occupational)	U.S. EPA 2004
Metallic Mercury	0.0002 mg/m^3	Chronic	Neurophysiological effects (occupational)	ATSDR 1999
Inorganic Mercury	N/A[1]	-	-	-
Organic Mercury	N/A[1]	-	-	-
Cancer Effects				
Metallic Mercury	N/A[1]	-	-	-
Inorganic Mercury	N/A[1]	-	-	-
Organic Mercury	N/A[1]	-	-	-

Note: [1]Not applicable

C5.3.3 Selected Exposure Limits

Table C5-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C5-3 Selected Exposure Limits for Mercury for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Methyl mercury	oral	non-carcinogenic	0.0001	mg/kg/d	Neurological effects (epidemiological study)	U.S. EPA 2004

C5.4 References

Agency for Toxic Substances Disease Registry (ATSDR) 1999. *Toxicological Profile for Mercury.* U.S. Department of Health and Human Services, Public Health Service, Atlanta, Georgia. March. http://www.atsdr.cdc.gov/toxprofiles/tp46.html (Accessed Oct. 12 2004).

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Health Canada 2003. *Federal Contaminated Site Risk Assessment in Canada. Part II: Health Canada Toxicological Reference Values (TRVs).* Version 1.0 October.

Health Canada 1979. *Guidelines for Canadian Drinking Water Quality - Supporting Documentation for Mercury.* Ottawa, ON. February. Original version April 1979, updated September 1986. http://www.hc-sc.gc.ca/hecs-sesc/water/dwgsup.htm (Accessed Oct. 12 2004).

Kjellstrom, T., P. Kennedy, S. Wallis *et al.* 1989. *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 2: Interviews and Psychological Tests at Age 6.* Natl Swed Environ Prot Bd, Rpt 3642 (Solna, Sweden).

Kjellstrom, T., P. Kennedy, S. Wallis et al. 1986. *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 1: Preliminary Test at Age 4.* Natl Swed Environ Protec Bd, Rpt 3080 (Solna, Sweden).

Myers, G.J., P.W. Davidson, C.F. Shamlaye *et al.* 1997. *Effects of Prenatal Methylmercury Exposure from a High Fish Diet on Developmental Milestones in the Seychelles Child Development Study.* Neurotoxicology 18(3): 819-830.

Myers, G.J., D.O. Marsh, C. Cox *et al.* 1995a. *A Pilot Neurodevelopmental Study of Seychellois Children Following in utero Exposure to Methylmercury from a Maternal Fish Diet.* Neurotoxicology 16(4): 629-638.

Myers, G.J., D.O. Marsh, P.W. Davidson. 1995b. *Main Neurodevelopmental Study of Seychellois Children Following in utero Exposure to Methylmercury from a Maternal Fish Diet: Outcome at Six Months.* Neurotoxicology 16(4): 653-664.

Myers, G.J., P.W. Davidson, C. Cox *et al.* 1995c. *Neurodevelopmetnal Outcomes of Seychellois Children Sixty-Six Months After in utero Exposure to Methylmercury from a Maternal Fish Diet: Pilot Study.* Neurotoxicology 16(4): 639-652.

United States Environmental Protection Agency (U.S. EPA) 2004. Integrated Risk Information System (IRIS). On-line database. http://www.epa.gov/iris/ (Accessed Oct. 12 2004) Mercuric chloride: Oral RfD assessment last revised May 1995, Inhalation RfC assessment last revised April 1994 and Carcinogenicity assessment last revised May 1995.. Elemental Mercury: Inhalation RfC assessment last revised June 1995 and Carcinogenicity assessment last revised May 1995. Methylmercury: Oral RfD assessment last revised July 2001. Inhalation RfC assessment last revised July 2001 and Carcinogenicity assessment last revised May 1995.

C6.0 Toxicological Profile for Thallium

Pure thallium is a soft, bluish-white metal that is widely distributed in trace amounts in the earth's crust. Pure thallium exists in nature but is usually found combined with other elements in inorganic compounds. Thallium forms compounds in both the monovalent and trivalent states; however, the monovalent state is the more stable.

Thallium is used mostly in the manufacture of electronic devices, switches, and closures. It also has limited use in the manufacture of special glasses and for medical procedures that evaluate heart disease.

C6.1 Pharmacokinetics

Limited data show direct gastrointestinal tract absorption in humans Both human and animal studies suggest that thallium is completely absorbed when ingested. (ATSDR 1992) Analysis of human tissues indicate that thallium is distributed throughout the body. In animals, distribution of thallium from the blood stream is rapid and widespread. Thallium was found to accumulate in the kidney followed by the heart, brain, bone, skin, and blood. The biological half-life for thallium was 3.3 days. (ATSDR 1992). Excretion of thallium is via feces and urine.

C6.2 Toxicology

C6.2.1 Non-Cancer Effects

Human occupational studies indicate that thallium may affect the nervous system following inhalation. (ATSDR 1992) Human case studies revealed that the nervous system is susceptible to thallium toxicity after acute oral exposure at high doses. Peripheral neuropathy was reported in thallium poisoning in China from 1960 to 1977 In animals, structural and functional changes were observed in peripheral nerves in rats following oral exposure. (ATSDR 1992)

Ingestion of thallium has been associated with hair loss in humans. (ATSDR 1992)

Thallium can cross the human placenta; however, data are limited regarding the developmental effects. (ATSDR 1992)

C6.2.2 Cancer Effects

There is limited information investigating carcinogenic endpoints from exposure to thallium. The studies available do not indicate potential carcinogenic impacts. (U.S. EPA 2004)

C6.2.3 Susceptible Populations

Limited toxicity data suggest there are certain subgroups of the general population which may be more susceptible to thallium exposure than other groups. People with pre-existing neurological disease, kidney, and liver damage may be at risk. (ATSDR 1992)

C6.3 Current Exposure Limits

Health Canada (2003) does not provide any exposure limits for thallium.

C6.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C6-1.

Non-Cancer

ATSDR (1992) did not develop any MRLs for oral exposure to thallium.

Thallium Sulphate

The U.S. EPA IRIS database (U.S. EPA 2004) provides an oral RfD of 8E-5 mg/kg/d. This value is based on a study of rats treated by gavage with an aqueous solution of thallium sulfate (U.S. EPA 1986). Apparent dose-related increases in the incidence of alopecia, lacrimation, and exophthalmos were observed throughout the study. A NOAEL was selected based on dose-related changes observed in some blood chemistry parameters: increased SGOT, LDH, and sodium levels, and decreased blood sugar levels. Based on the results of this study the 0.25 mg/kg/day thallium sulfate is considered a NOAEL. The RfD is then derived by dividing the NOAEL by an uncertainty factor (UF) of 3000 (10 to extrapolate from subchronic to chronic data, 10 for intraspecies extrapolation and 10 to account for interspecies variability, and a factor of 3 to account for lack of reproductive and chronic toxicity data). The overall confidence in this RfD is low.

Thallic oxide

The U.S. EPA (2004) does not provide any exposure limits.

Thallium acetate

The U.S. EPA (2004) provides an RfD of 9E-5 mg/kg/d based on the thallium sulphate study.

Thallium carbonate

The U.S. EPA (2004) provides an RfD of 8E-5 mg/kg/d based on the thallium sulphate study.

Thallium chloride

The U.S. EPA (2004) provides an RfD of 8E-5 mg/kg/d based on the thallium sulphate study.

Thallium nitrate

The U.S. EPA (2004) provides an RfD of 9E-5 mg/kg/d based on the thallium sulphate study.

Carcinogenic

The U.S. EPA (2004) has classified the potential carcinogenicity of thallium salts as D; not classifiable as to human carcinogenicity. Therefore, no slope factor is provided.

Table C6-1 Oral Exposure Limits for Thallium Compounds

Thallium Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Thallium sulphate	8×10^{-5}	chronic	changes in blood chemistry parameters (SGOT, LDH, and sodium) and decreased blood sugar levels (rat study)	US EPA 2004
Thallic oxide	--[1]			US EPA 2004
Thallium acetate	9×10^{-5}		same as thallium sulphate	US EPA 2004
Thallium carbonate	8×10^{-5}		same as thallium sulphate	US EPA 2004
Thallium chloride	8×10^{-5}		same as thallium sulphate	US EPA 2004
Thallium nitrate	9×10^{-5}		same as thallium sulphate	US EPA 2004
Cancer Effects				
Thallium sulphate	NA[2]			
Thallic oxide	NA			
Thallium acetate	NA			
Thallium carbonate	NA			
Thallium chloride	NA			
Thallium nitrate	NA			

Note: 1 No data
2 Not applicable

C6.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C6-2.

Non-Cancer

No exposure limit for inhalation was obtained from the reviewed sources (U.S. EPA 2004, ATSDR 1992, Health Canada 2003).

Carcinogenic

The U.S. EPA (2004) has classified the potential carcinogenicity of thallium salts as D; not classifiable as to human carcinogenicity. Therefore, no slope factor is provided.

Table C6-2 Inhalation Exposure Limits for Thallium Compounds

Thallium Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Thallium sulphate	--[1]			
Thallic oxide	--			
Thallium acetate	--			
Thallium carbonate	--			
Thallium chloride	--			
Thallium nitrate	--			
Cancer Effects				
Thallium sulphate	NA[2]			
Thallic oxide	NA			
Thallium acetate	NA			
Thallium carbonate	NA			
Thallium chloride	NA			
Thallium nitrate	NA			

Note: 1 No data
2 Not applicable

C6.3.3 Selected Exposure Limits

Table C6-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C6-3 Selected Exposure Limits for Thallium for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Thallium	oral	non-carcinogenic	8×10^{-5}	mg/kg/d	changes in blood chemistry parameters (SGOT, LDH, and sodium) and decreased blood sugar levels (rat study)	U.S. EPA 2004

C6.4 References

Agency for Toxic Substances and Disease Registry (ATSDR) 1992. *Toxicological Profile for Thallium.* Draft. U.S. Department of Health and Human Services. September

Health Canada 2003. *Federal Contaminated Site Risk Assessment in Canada. Part II: Health Canada Toxicological Reference Values (TRVs).* Version 1.0 October.

United States Environmental Protection Agency (U.S. EPA) 2004. *IRIS - Integrated Risk Information System.* On-line database. http://www.epa.gov/iris/

United States Environmental Protection Agency (U.S. EPA) 1986. *Subchronic (90-day) Toxicity of Thallium Sulfate in Sprague-Dawley Rats.* Office of Solid Waste, Washington, DC. (cited in U.S. EPA 2004)

C7.0 Toxicological Profile for Zinc

Zinc is an abundant element and constitutes approximately 0.004 percent of the Earth's substance. The main use for zinc in Canada is for galvanizing iron and steel (approximately 40%). A further 20% goes towards the production of brass plumbing and heating fittings and 15% percent was used in the die-casting industry to produce builders'hardware and automobile fittings. The remaining consumption of zinc is divided among many industries (e.g. manufacture of paints, rubber, printing, wood preservatives and pesticides). (Health Canada 2002)

C7.1 Pharmacokinetics

Zinc is an essential nutrient that is necessary for the function of a large number of metalloenzymes. Health Canada refers to a Recommended Daily Allowance (RDA) ranging from 3 mg/day to 8 mg/d for children depending on the age and sex and, from the age of 9, 11 mg/day for males and 8 mg/day for females. The RDA is an estimate of the zinc needed to meet the nutrient requirements of nearly all (97 to 98%) of healthy individuals (NAS 2002).

In humans, zinc is absorbed in the small intestine by a carrier-mediated mechanism. Generally, 33 percent is accepted as the average zinc absorption in humans (Health Canada 2002). At high doses, zinc and iron appear to antagonize each others' absorption. In addition, excessive levels of both tin and copper in the diet may reduce zinc absorption. Zinc absorbed from the intestine is carried to the liver bound to albumin.

Within the circulatory system, between 80 and 90 percent of the zinc found in whole blood is in the erythrocytes, where it is largely bound to carbonic anhydrase. The remaining plasma zinc is primarily bound to albumin, although other proteins and free amino acids also bind zinc. (Health Canada 2002). Muscle and bone contain approximately 90% of the total amount of zinc in the body (60% and 30%, respectively) (ATSDR 2003)

Zinc is primarily excreted via the gastrointestinal tract; zinc excreted in this way consists of unabsorbed dietary zinc, endogenous zinc secreted into the gastrointestinal tract, and zinc from mucosal cell desquamation.(Health Canada 2002) Excretory mechanisms contribute to zinc homeostasis; however, regulation of zinc absorption is the major homeostatic mechanism. Under normal circumstances, about 0.5 mg of zinc may be lost in perspiration, and about an equal amount is lost in daily urine. (Health Canada 2002)

C7.2 Toxicology

C7.2.1 Non-Cancer Effects

There are differences in toxicity between the various zinc compounds following inhalation exposure. Acute exposure can result in metal fume fever, induced by intense inhalation of metal oxides, especially zinc. Zinc chloride, a corrosive inorganic salt, is damaging to the mucous membranes of the nasopharynx and respiratory tract upon contact. Humans acutely exposed to zinc ammonium sulfate exhibited minimal or no short-term respiratory effects. There are potential hematological effects following inhalation exposure to zinc. Leukocytosis persisting for approximately 12 hours after fever dissipates is one of the hallmarks of metal fume fever (ATSDR 2003).

A number of reports involving acute exposure to zinc suggest that the gastrointestinal tract and the pancreas are end points of concern, and that the adrenal cortex and central nervous system may also be affected. (ATSDR 2003)

Zinc supplementation can alter the copper balance (U.S. EPA 2004). The effects on copper and iron biochemistry are considered of concern since long-term iron or copper deficiency could result in significant adverse effects. For example, zinc supplementation therapy with megadoses of up to 5 g/day, as well as smaller amounts of 150 mg/day, taken for 1 to 2 years have produced copper deficiency anemia (Fischer et al., 1984). In addition, several studies have investigated the effects of zinc supplementation on the high-density lipoprotein (HDL) levels of adult males. These have been added as supporting studies because the observed change in HDL values in males may be significant since a sustained decrease in HDL concentrations may be associated with increased risk of coronary artery disease when combined with a parallel increase in low-density lipoprotein (LDL) cholesterol (U.S. EPA 2004).

Some evidence suggests the possibility of teratogenic effects due to oral exposure to zinc (ATSDR 2003, Health Canada 2002).

Zinc plays a role in the normal development and maintenance of the immune system, such as in the lymphocyte response to mitogens and as a cofactor for the thymic hormone thymulin. Oral exposure to zinc at levels much higher than the RDA has impaired immune and inflammatory responses. (ATSDR 2003, Health Canada 2002)

Genotoxicity studies conducted in a variety of test systems have failed to provide evidence for mutagenicity of zinc. However, there are indications of weak clastogenic effects following zinc exposure. (ATSDR 2003)

C7.2.2 Cancer Effects

There are no reports on the possible carcinogenicity of zinc and compounds per se in humans. (U.S. EPA 2004) There are reports which compare zinc levels in normal and cancerous tissue. Studies of occupational exposure to zinc compounds have also been conducted, but have limited value because they do not correlate exposure with cancer risk. There is inadequate evidence from animal studies to assess carcinogenicity. There is some evidence that zinc may be a modifier of the carcinogenic response; zinc deficiency or excessively high levels of zinc may enhance susceptibility to carcinogenesis, whereas supplementation with low to moderate levels of zinc may offer protection (Woo et al., 1988).

C7.2.3 Susceptible Populations

Data are not presently sufficient to determine whether children are more sensitive to these effects than adults. (ATSDR 2003).

C7.3 Current Exposure Limits

C7.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C7-1.

Non-Cancer

The U.S. EPA IRIS database (U.S. EPA 2004) provides an oral RfD of 0.3 mg/kg/d. This value is based on a 47% decrease in erthrocyte superoxide dismutase (ESOD) concentration in adult females after 10 weeks of zinc exposure (Yadrick et al. 1989). Change in enzyme activity is considered a better indicator of altered copper status than a measure of metal concentration in tissue or plasma. The LOAEL of 1.0 mg/kg-day was calculated from the sum of these dietary estimates and the supplemental zinc dose using an assumed body weight of 60 kg for adult females. The RfD is then derived by dividing the LOAEL by an uncertainty factor (UF) of 3 (based on a minimal LOAEL from a moderate-duration study of the most sensitive humans and consideration of a substance that is an essential dietary nutrient). The overall confidence in this RfD is medium.

ATSDR (2003) did not develop an acute-duration MRLs because of a lack of appropriate data on effects. An intermediate-duration (15-365 days) and chronic MRL of 0.3 mg/kg/d has been derived based on hematological effects, specifically decreases in erythrocyte superoxide dismutase activity, serum ferritin, and hematocrit, in women

given daily supplements of zinc as zinc gluconate for 10 weeks (Yadrick et al. 1989). Health Canada (2003) does not provide a TRV for zinc.

Carcinogenic

The U.S. EPA (2004) has classified the potential carcinogenicity of zinc as D; not classifiable as to human carcinogenicity. Therefore, no slope factor is provided.

Table C7-1 Oral Exposure Limits for Zinc Compounds

Zinc Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Zinc compounds	0.3	chronic	decrease in erthrocyte superoxide dismutase (ESOD) concentration in adult females	US EPA 2004
Zinc compounds	0.3	Intermediate/ chronic	hematological effects	ATSDR 2003
Cancer Effects				
Zinc compounds	NA[1]			

Note: [1]Not applicable

C7.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C7-2.

Non-Cancer

No exposure limit for inhalation was obtained from the reviewed sources (U.S. EPA 2004, ATSDR 2003, Health Canada 2003).

Carcinogenic

The U.S. EPA (2004) has classified the potential carcinogenicity of zinc as D; not classifiable as to human carcinogenicity. Therefore, no slope factor is provided.

Table C7-2 Inhalation Exposure Limits for Zinc Compounds

Zinc Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Zinc and compounds	--[1]			
Cancer Effects				
Zinc and compounds	NA[2]			

Note: 1 No data
2 Not applicable

C7.3.3 Selected Exposure Limits

Table C7-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C7-3 Selected Exposure Limits for Zinc for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Zinc	oral	non-carcinogenic	0.3	mg/kg/d	decrease in erthrocyte superoxide dismutase (ESOD) concentration in adult females	U.S. EPA 2004

C7.4 References

Agency for Toxic Substances and Disease Registry (ATSDR) 2003. *Toxicological Profile for Zinc.* Draft. U.S. Department of Health and Human Services. September

Fischer, P.W.F., A. Giroux and A.R. L'Abbe. 1984. *Effect of Zinc Supplementation on Copper Status in Adult Man.* Am. J. Clin. Nutr. 40: 743-746. (cited in U.S. EPA 2004)

Health Canada 2003. *Federal Contaminated Site Risk Assessment in Canada. Part II: Health Canada Toxicological Reference Values (TRVs).* Version 1.0 October.

Health Canada 2002. *Guidelines for Canadian Drinking Water Quality - Supporting Documentation.* Ottawa, ON. http://www.hc-sc.gc.ca/hecs-sesc/water/dwgsup.htm

National Academy Press (NAS) 2002. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc.* Food and Nutrition Board, Institute of Medicine, Washington DC. http://books.nap.edu/books/0309072794/html/index.html

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Woo, Y.T., D.Y. Lai, J.C. Arcos and M.F. Argus. 1988. *Chemical Induction of Cancer: Structural Bases and Biological Mechanisms.* Vol. IIIC, Natural, Metal, Fiber and Macromolecular Carcinogens. Academic Press, San Diego. p. 488-489. (cited in U.S. EPA 2004)

Yadrick, M.K., M.A. Kenney and E.A. Winterfeldt. 1989. *Iron, Copper, and Zinc Status: Response to Supplementation With Zinc or Zinc and Iron in Adult Females.* Am. J. Clin. Nutr. 49: 145-150. (cited in U.S. EPA 2004 and ATSDR 2003)

C8.0 Toxicological Profile for Dioxins and Furans

Dioxins and furans are a group of chlorinated compounds that that share certain similar chemical structures and mode-of-action biological characteristics. A total of 30 of these dioxin-like compounds exist and are members of three closely related families: the chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated dibenzofurans (CDFs) and certain polychlorinated biphenyls (PCBs). The term dioxin is also used for the most well-studied and one of the most toxic dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

There has been significant work complete on the toxicity of this group of compounds which is currently under evaluation. The U.S. Environmental Protection Agency is progressing toward completion of its comprehensive reassessment of dioxin exposure and human health effects. As recently as October 2004 a draft review of the assessment was released (U.S. EPA 2004a) in preparation for the first meeting of the NAS panel scheduled for November 2004. As the understanding of the toxicity of this group of compounds is currently evolving a detailed toxicological profile was not prepared however a review of the current exposure limits is provided.

C8.1 Current Exposure Limits

C8.3.1 Oral Exposure Limits

For a summary of oral exposure limits, see Table C8-1.

Non-Cancer

The U.S. EPA IRIS database (U.S. EPA 2004b) does not provide any exposure limits for dioxins or furans.

ATSDR (1998) provides an acute-duration MRL of 0.0002 (2×10^{-4}) µg/kg/day for oral exposure (14 days or less) to 2,3,7,8-TCDD. The acute duration oral MRL was based on a NOAEL of 0.005 µg/kg and a LOAEL of 0.01 µg/kg for immunological effects in female mice (Burleson et al. 1996). An MRL of 0.00002 (2×10^{-5}) µg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 2,3,7,8-TCDD. The intermediate-duration oral MRL was based on a NOAEL of 0.0007 µg/kg/day for immunological effects in Hartley guinea pigs fed 2,3,7,8-TCDD in the diet for 90 days (DeCaprio et al. 1986). An MRL of 0.000001 (1×10^{-6}) µg/kg/day has been derived for

chronic-duration oral exposure (365 days or more) to 2,3,7,8-TCDD. The chronic-duration oral MRL is based on a LOAEL of 0.00012 µg/kg/day for developmental toxicity in rhesus monkeys (Schantz et al. 1992).

ATSDR (1994) derived an acute-duration MRL of 0.001 µg/kg/day for oral exposure (14 days or less) to 2,3,4,7,8-pentaCDF. The acute oral MRL was based on a LOAEL for mild thymic lymphoid hypoplasia identified in groups of Hartley guinea pigs (Moore et al. 1979). An MRL of 0.00003 µg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to 2,3,4,7,8pentaCDF. The intermediate oral MRL was based on a LOAEL for hepatic effects (increased serum bilirubin, decreased serum triglycerides) identified in rats (Pluess et al. 1988; Poiger et al. 1989). An MRL for chronic-duration oral exposure was not derived for CDFs due to a lack of appropriate human and animal data.

Officially, the Health Canada TDI for dioxins and furans is 10 pg/kg-d (Health Canada 1996); however the WHO/FAO Joint Expert Committee on Food Additives and Contaminants recently proposed a revised TDI of 2 pg/kg-d (WHO JECFA 2002). The Food Directorate, Health Canada, generally endorses and applies the TDIs for food contaminants derived by the JECFA and therefore it is recommended in Health Canada (2003) that the lower TDI be used.

Carcinogenic

The U.S. EPA (2004b) has classified the potential carcinogenicity of hexachlorodibenzo-p-dioxin, mixture (HxCDD) as B2; probable human carcinogen based on hepatic tumors in mice and rats by gavage. A slope factor of 6.2E+3 per (mg/kg)/day was derived.

Table C8-1 Oral Exposure Limits for Dioxins and Furans

	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Dioxins and Furans	2×10^{-9} mg/kg/d	chronic	Reproductive effects	WHO JECFA 2002
2,3,7,8-TCDD	2×10^{-7} mg/kg/d	acute	immunological effects (mice)	ATSDR 1998
2,3,7,8-TCDD	2×10^{-8} mg/kg/d	intermediate	immunological effects (guinea pigs)	ATSDR 1998
2,3,7,8-TCDD	1×10^{-9} mg/kg/d	chronic	developmental toxicity (rhesus monkeys)	ATSDR 1998
2,3,4,7,8-pentaCDF	1×10^{-6} mg/kg/d	acute	thymic lymphoid hypoplasia (guinea pigs)	ATSDR 1994
2,3,4,7,8-pentaCDF	3×10^{-8} mg/kg/d	intermediate	hepatic effects (rats)	ATSDR 1994
Cancer Effects				
HxCDD	6200 $(mg/kg/d)^{-1}$	chronic	Hepatic tumors	U.S. EPA 2004b

C8.3.2 Inhalation Exposure Limits

For a summary of inhalation exposure limits, see Table C8-2.

Non-Cancer

No exposure limit for inhalation was obtained from the reviewed sources (U.S. EPA 2004b, ATSDR 1998, 1994, Health Canada 2003).

Carcinogenic

No exposure limit for the carcinogenic effects of inhalation was obtained from the reviewed sources.

Table C8-2 Inhalation Exposure Limits for Dioxins and Furans

Compound	Exposure Limit	Toxicological Basis		Regulatory Agency
		Exposure Duration	Endpoint	
Non-Cancer Effects				
Dioxins and Furans	--[1]			
Cancer Effects				
Dioxins and Furans	--[1]			

Note: 1 No data
2 Not applicable

C8.3.3 Selected Exposure Limits

Table C8-3 shows the toxicity reference values that were selected for use in the Belledune Area Health Study.

Table C8-3 Selected Exposure Limits for Dioxins and Furans for the Belledune Area Health Study

	Pathway	Effect	TRV Value	Units	Endpoint	Reference
Dioxins and furans	oral	non-carcinogenic	2×10^{-9}	mg/kg/d	Provisional TDI for reproductive effects based on the mid-point of values from a range of studies.	WHO JECFA 2002

C8.4 References

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